Access DB# 90823

# SEARCH REQUEST FORM

**Scientific and Technical Inf rmation Center**

Requester's Full Name: Jeffrey Srew Examiner #: 74907 Date: 4/7/03
Art Unit: 1637 Phone Number 30 5-3886 Serial Number: 09/835371
Mail Box and Bldg/Room Location: 10 B 03 Results Format Preferred (circle): PAPER DISK E-MAIL

**If mor than one search is submitted, please prioritize searches in order of need.**

**********

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Polyamide Nucleic Acid Derivatives

Inventors (please provide full names): Uhlmann

Earliest Priority Filing Date: 4/17/01

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

elected Gaps 1-25, 30-32, 40-80

When done, give me a call
703-305-3886
to go over case + 09/835370
will stop by
thanks
Jeff

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

**********

| STAFF USE ONLY | Type of Search | | Vendors and cost where applicable | |
|---|---|---|---|---|
| Searcher: | NA Sequence (#) | | STN | ✓ |
| Searcher Phone #: 4498 | AA Sequence (#) | | Dialog | |
| Searcher Location: | Structure (#) | ✓ | Questel/Orbit | |
| Date Searcher Picked Up: 4/22/03 | Bibliographic | ✓ | Dr.Link | |
| Date Completed: 4/22/03 | Litigation | | Lexis/Nexis | |
| Searcher Prep & Review Time: | Fulltext | | Sequence Systems | |
| Clerical Prep Time: 30 | Patent Family | | WWW/Internet | |
| Online Time: +45 | Other | | Other (specify) | |

PTO-1590 (8-01)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 12:00:37 ON 12 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

```
Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   11 APR 2003  HIGHEST RN 502793-56-8
DICTIONARY FILE UPDATES:  11 APR 2003  HIGHEST RN 502793-56-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l13
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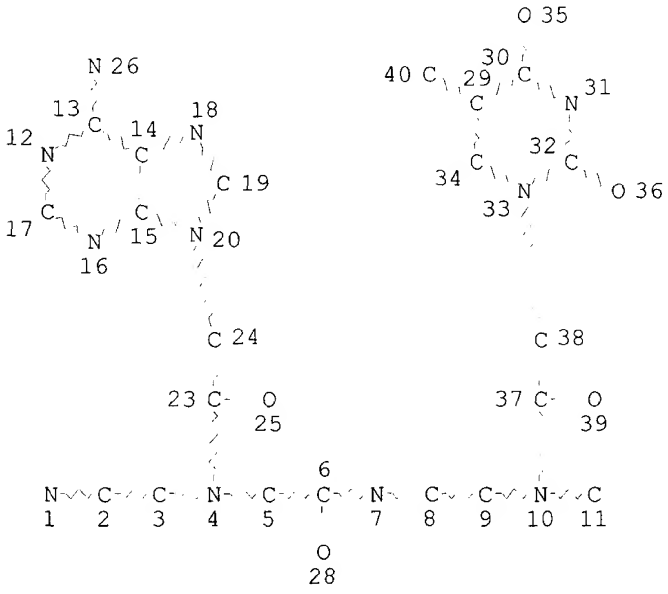


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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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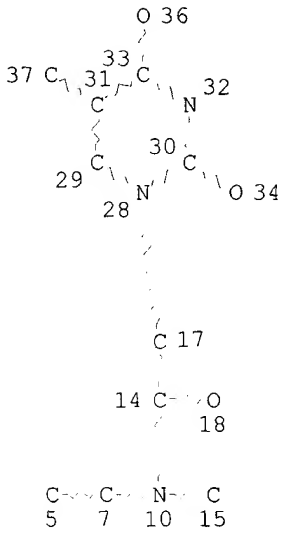


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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
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L11 2 SEA FILE=REGISTRY ABB=ON PLU=ON L10 AND 6/NR
L13 1 SEA FILE=REGISTRY ABB=ON PLU=ON L11 NOT OC5-C6/ES

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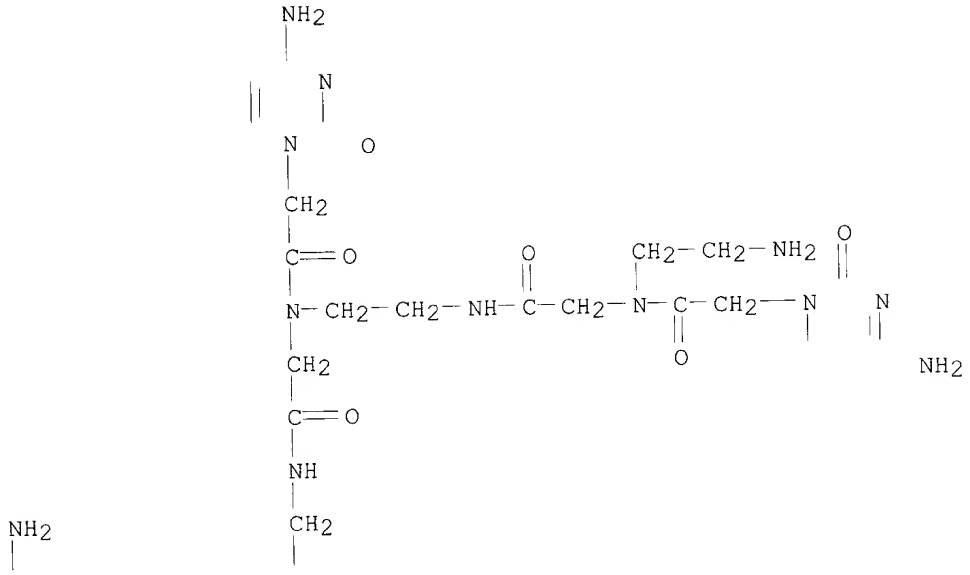
L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 189444-22-2 REGISTRY
CN Peptide nucleic acid, (H-C-C-A-T-T)-OH (9CI) (CA INDEX NAME)
FS NUCLEIC ACID SEQUENCE
MF C53 H69 N25 O17
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

PAGE 1-A



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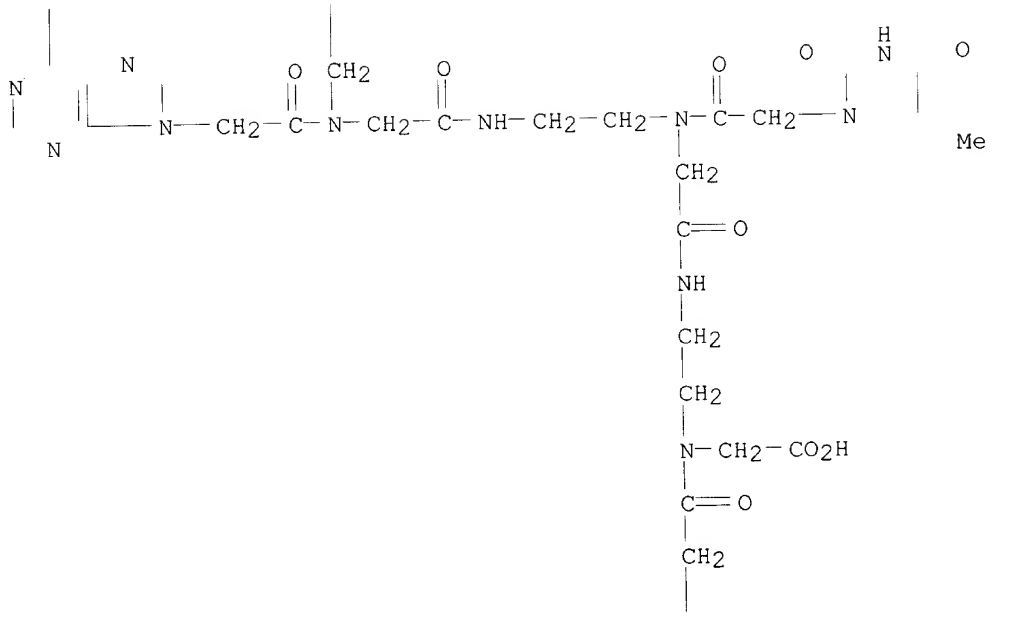

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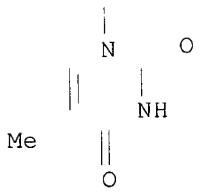

1 REFERENCES IN FILE CA (1962 TO DATE)
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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 126:326433

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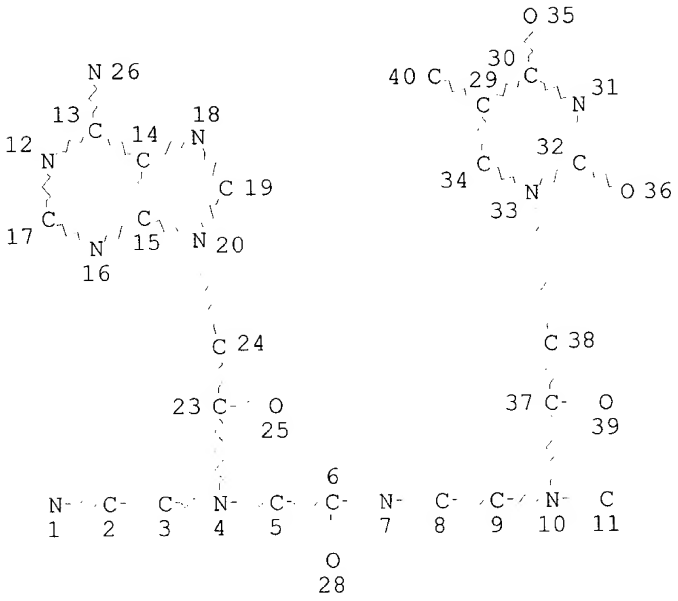

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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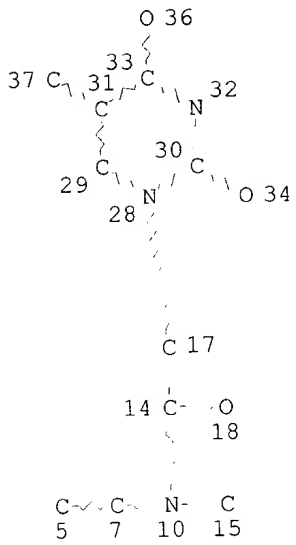


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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L5 1080 SEA FILE=REGISTRY SSS FUL L3
L10 57 SEA FILE=REGISTRY SUB=L5 SSS FUL L1
L12 2 SEA FILE=REGISTRY ABB=ON PLU=ON L10 AND 7/NR
L14 1 SEA FILE=REGISTRY ABB=ON PLU=ON L12 NOT 46.150.18/RID

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L14 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 213272-49-2 REGISTRY
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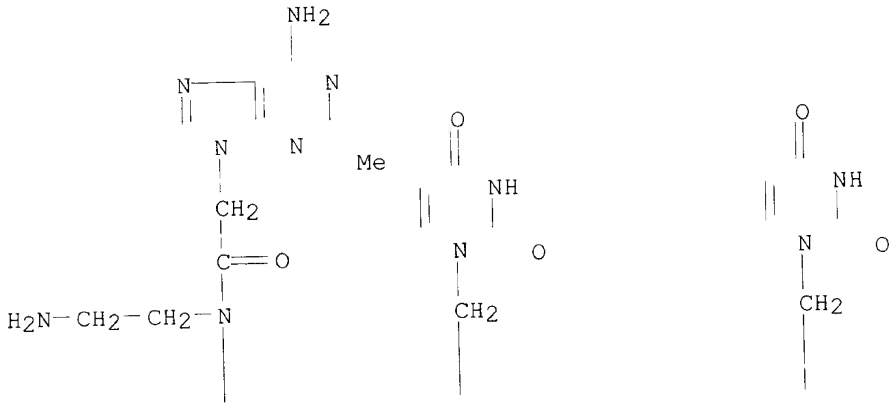
FS NUCLEIC ACID SEQUENCE
MF C54 H69 N27 O17
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



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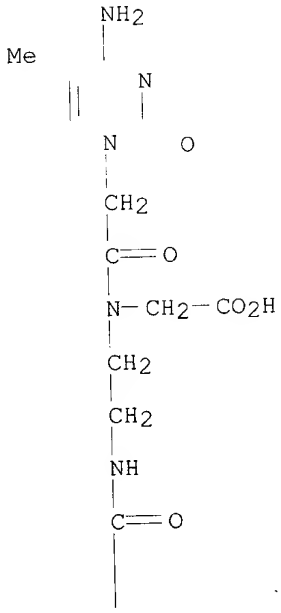

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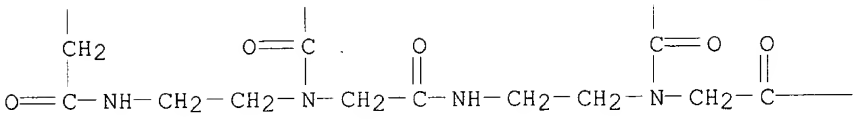

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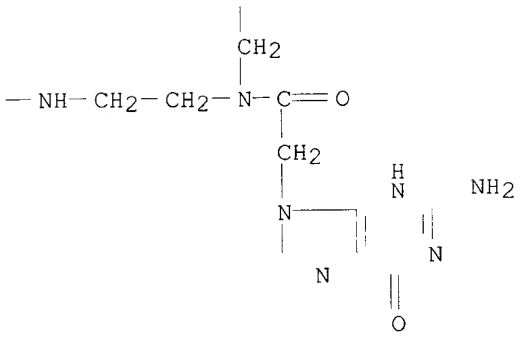

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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 129:257138

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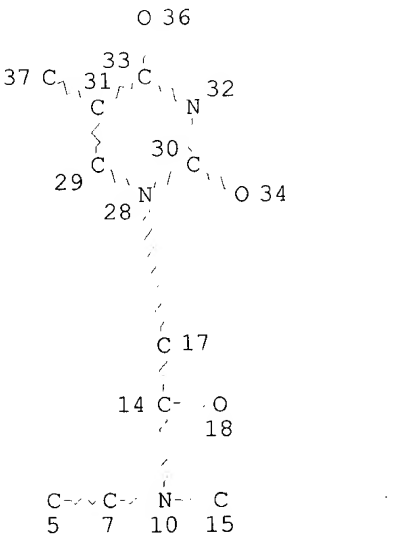

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

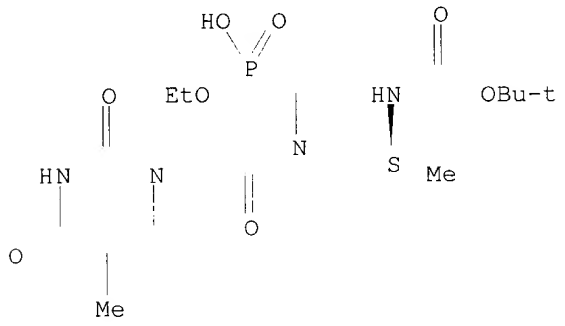
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L5 1080 SEA FILE=REGISTRY SSS FUL L3
L15 208 SEA FILE=REGISTRY ABB=ON PLU=ON L5 AND P/ELS
L16 122 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND 1/P
L17 4 SEA FILE=REGISTRY ABB=ON PLU=ON L16 AND 1/NR

=> d ide can tot l17

L17 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 403517-90-8 REGISTRY
CN 8-Oxa-2,5-diaza-7-phosphadecanoic acid, 5-[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl]-7-hydroxy-3-methyl-, 1,1-dimethylethyl ester, 7-oxide, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C18 H31 N4 O8 P**
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.



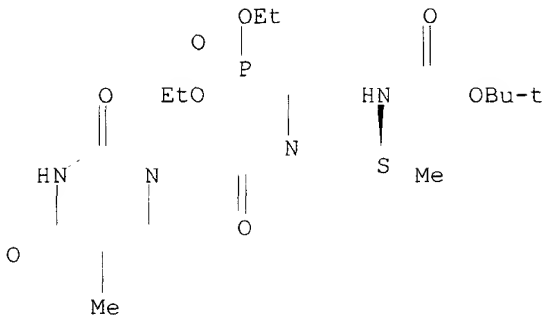
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:232515

L17 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 403517-87-3 REGISTRY
CN 8-Oxa-2,5-diaza-7-phosphadecanoic acid, 5-[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl]-7-ethoxy-3-methyl-, 1,1-dimethylethyl ester, 7-oxide, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C20 H35 N4 O8 P**
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

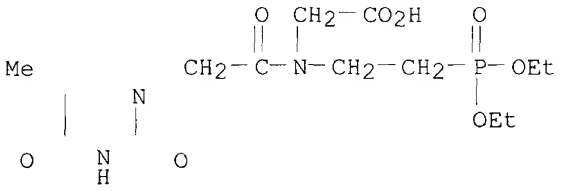


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:232515

L17 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 329326-33-2 REGISTRY
CN Glycine, N-[2-(diethoxyphosphinyl)ethyl]-N-[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C15 H24 N3 O8 P**
SR CA
LC STN Files: CA, CAPLUS, CASREACT



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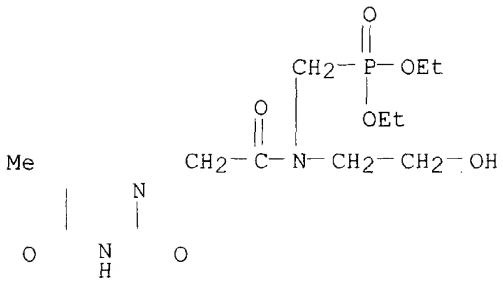
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:222969

L17 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 183057-72-9 REGISTRY
CN Phosphonic acid, [[[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl](2-hydroxyethyl)amino]methyl]-, diethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C14 H24 N3 O7 P**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 126:118140

REFERENCE 2: 126:100903

REFERENCE 3: 125:301493

=> d his

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L2 STR
L3 STR L2
L4 50 S L3
L5 1080 S L3 FUL
SAV L5 SIEW835/A
L6 STR L2
L7 0 S L6 CSS SAM SUB=L5
L8 0 S L6 CSS FUL SUB=L5
SAV L8 SIEW835A/A
L9 1 S L1 SAM SUB=L5
L10 57 S L1 FUL SUB=L5
SAV L10 SIEW835B/A
L11 2 S L10 AND 6/NR
L12 2 S L10 AND 7/NR
L13 1 S L11 NOT OC5-C6/ES
L14 1 S L12 NOT 46.150.18/RID
L15 208 S L5 AND P/ELS
L16 122 S L15 AND 1/P
L17 4 S L16 AND 1/NR

FILE 'REGISTRY' ENTERED AT 12:00:37 ON 12 APR 2003

FILE 'HCAPLUS' ENTERED AT 12:01:57 ON 12 APR 2003
L18 7 S L13,L14,L17
L19 3 S L18 AND (UHLMANN ? OR BREIPOHL ? OR WILL D?)/AU
L20 3 S L18 AND HOECHST?/PA,CS
L21 3 S L19,L20
E US20020187473/PN
L22 1 S E3
SEL RN

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L26            2 S L23 NOT UNSPECIFIED
L27           61 S L23 NOT L26
L28           11 S L27 AND PEPTIDE
L29            5 S L28 AND 22/SQL
L30            6 S L28 NOT L29
L31            4 S L30 NOT ISOBENZOFURAN
L32            3 S L31 NOT THIENO
L33           50 S L27 NOT L28

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                E UHLMANN E/AU
L34          179 S E3,E4,E14-E18
                E UEHLMANN E/AU
                E BRIEPOHL G/AU
                E BREIPOHL G/AU
L35          106 S E3-E6
                E BREIPOEHL G/AU
L36            1 S E2
                E WILL D/AU
L37           40 S E3,E7-E10
L38          275 S L34-L37
L39          274 S L38 NOT L22
                E PEPTIDE NUCLEIC ACID/CT
                E E4+ALL
L40         1717 S E3+NT
                E E2+ALL
L41         4496 S PEPTIDE(S)NUCLEIC ACID
L42         5022 S PNA
L43         8250 S L40-L42
L44        38606 S ?PEPTIDE?(S)(?NUCLEO? OR ?NUCLEI?)
L45        42349 S L43,L44
L46           37 S L38 AND L45
L47            7 S L18-L22 AND L45
L48            3 S L47 AND L38
L49            8 S L18-L22,L47,L48
L50           34 S L46 NOT L49

=> d 149 all hitstr tot

L49  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2003 ACS
AN   2001:814939  HCAPLUS
DN   136:232515
TI   Synthesis of chiral phosphono-peptide nucleic
     acid monomers
AU   Wu, Yun; Xu, Jie-Cheng
CS   Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
     Shanghai, 200032, Peop. Rep. China
SO   Huaxue Xuebao (2001), 59(10), 1660-1666
     CODEN: HHHPA4; ISSN: 0567-7351
PB   Kexue Chubanshe
DT   Journal
LA   Chinese
CC   34-2 (Amino Acids, Peptides, and Proteins)
OS   CASREACT 136:232515
AB   Peptide nucleic acids are the potential
     candidate of antisense and antigene.  Chiral monomer backbones were
     efficiently prepd. by reductive amination of N-Boc or N-Fmoc protected
     L-alaninal with aminomethylphosphate di-Et ester and subsequent acylation
```

of free secondary amines with thymine-1-ylacetic acid. After chem. switch of N-Boc to N-Fmoc, protected chiral phosphono-**PNA** monomers were obtained.

ST amino phosphono nucleic acid prepn

IT Human
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

IT **Nucleic** acids
**Peptide nucleic acids**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of chiral **phosphonopeptide nucleic acid** monomers)

IT 101-02-0, Triphenyl phosphite 621-84-1 15761-38-3 20924-05-4 28920-43-6 35661-39-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

IT 50917-72-1P 70908-61-1P 77393-49-8P 79069-50-4P 87694-49-3P 146803-41-0P 198542-03-9P 403517-85-1P 403517-86-2P **403517-87-3P** 403517-88-4P **403517-90-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

IT 76-05-1, Trifluoroacetic acid, reactions 109-02-4, N-Methylmorpholine 6638-79-5 13455-21-5, Potassium fluoride dihydrate 24608-52-4, tert-Butyl chloroformate 67126-19-6 403517-91-9
RL: RGT (Reagent); RACT (Reactant or reagent)
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

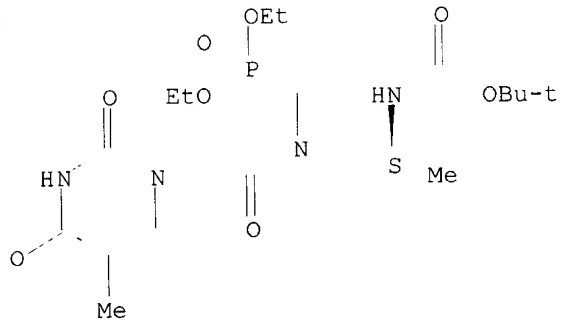
IT 403517-89-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

IT **403517-87-3P 403517-90-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of chiral **phosphonopeptide nucleic** acid monomers)

RN 403517-87-3 HCAPLUS

CN 8-Oxa-2,5-diaza-7-phosphadecanoic acid, 5-[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl]-7-ethoxy-3-methyl-, 1,1-dimethylethyl ester, 7-oxide, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

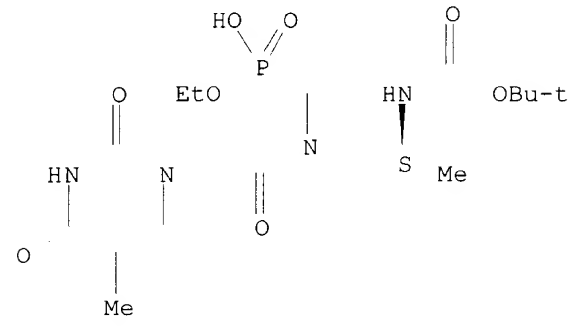



RN 403517-90-8 HCAPLUS

CN 8-Oxa-2,5-diaza-7-phosphadecanoic acid, 5-[(3,4-dihydro-5-methyl-2,4-dioxo-

1(2H)-pyrimidinyl)acetyl]-7-hydroxy-3-methyl-, 1,1-dimethylethyl ester, 7-oxide, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Applicant

L49 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:780897 HCAPLUS
DN 135:331677
TI Methods for preparing phosphorylated **peptide nucleic acids** carrying one or more marker, crosslinking, intracellular uptake, or binding affinity groups
IN **Uhlmann, Eugen; Breipohl, Gerhard; Will, David William**
PA Aventis Pharma Deutschland G.m.b.H., Germany
SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C07H
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 6, 33, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2001079216 | A2 | 20011025 | WO 2001-EP4030 | 20010407 |
| | WO 2001079216 | A3 | 20020228 | | |
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| | DE 10019135 | A1 | 20011031 | DE 2000-10019135 | 20000418 |
| | AU 2001054795 | A5 | 20011030 | AU 2001-54795 | 20010407 |
| | EP 1276760 | A2 | 20030122 | EP 2001-927897 | 20010407 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| | BR 2001010110 | A | 20030211 | BR 2001-10110 | 20010407 |
| | US 2002187473 | A1 | 20021212 | US 2001-835371 | 20010417 <-- |
| | NO 2002004959 | A | 20021015 | NO 2002-4959 | 20021015 |
| PRAI | DE 2000-10019135 | A | 20000418 | | |
| | WO 2001-EP4030 | W | 20010407 | | |

OS MARPAT 135:331677
AB The invention relates to **PNA** derivs. that carry one or more phosphoryl groups at the C terminus or at the C and N terminus of the

**PNA** backbone, said phosphoryl groups optionally carrying one or more marker groups, or groups for crosslinking, or groups that promote the intracellular uptake, or groups that improve the binding affinity of the **PNA** deriv. to nucleic acids. The invention further relates to a method for producing the above **PNA** derivs. and to the use thereof as a medicament or diagnostic agent. Thus, title compd. CH3(CH2)15OP(O)(OH)-T(oeg)[ATTCCGTCAT](CH2)6NHP(O)(OH)O-CH2CH(CH2OH)(CH2)4NHC(S)NH-fluorescein (I) [T(oeg) = O(CH2)2N(C(O)CH2-Base)CH2C(O)-; remainder of chain = normal **peptide** **nucleic acid** backbone] was prepd. using solid-phase **peptide** synthesis techniques. Hybridization tests of I with complementary DNA and RNA showed better complexation with DNA than with RNA, though both were stronger than with **PNA** Ac-NH-TATTCCGTCAT-(CH2)6NH2 ref. In vitro cell proliferation studies using I and human pre-B leukemia cells showed stronger inhibition than a known phosphorothioate oligonucleotide (no data).

ST **PNA** deriv prepn antiviral antimicrobial antitumor diagnostic hybridization

IT Diagnosis
(agents; prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT Solid phase synthesis
(peptide; prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT Antimicrobial agents
Antitumor agents
Antiviral agents
Biosensors
Nucleic acid hybridization
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT **Peptide nucleic acids**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT 368505-39-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT 367985-20-4P 367985-21-5P 367985-22-6P 367985-23-7P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT 367985-17-9P 367985-19-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT 367985-18-0P 368505-37-7P 368505-38-8P 368505-40-2P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **PNA** derivs. as therapeutic or diagnostic agents)

IT 110616-00-7 116364-61-5 147178-75-4 159845-57-5 169025-57-4, GenBank AR029142 181988-02-3 181988-09-0 186070-79-1, GenBank A42375 186071-78-3 186108-31-6, 3: PN: WO0004034 SEQID: 3 unclaimed DNA 186123-93-3, GenBank A44395 186162-52-7 186162-55-0, GenBank A42368 189356-60-3 195184-07-7, GenBank A42342 195184-11-3, GenBank A42347 195184-12-4 195184-14-6, GenBank A42351 195184-15-7, GenBank A42352 195184-16-8, GenBank A44386 195184-17-9, GenBank A42354 195184-18-0, GenBank A42355 195184-19-1, GenBank A42356 195184-20-4, GenBank A42357 195184-21-5, GenBank A42358 195184-22-6, GenBank A42359 195184-23-7, GenBank A42361 195184-24-8, GenBank A42362 195184-25-9, GenBank A42363

195184-26-0, GenBank A47186 195184-27-1 195184-28-2, GenBank A47179
197831-18-8 246223-25-6 257601-47-1, GenBank AX283184 325605-36-5,
GenBank AX283169 325605-37-6, GenBank AX283174 325605-38-7
325605-39-8 325605-40-1 325605-41-2 325605-42-3 325605-43-4
325605-44-5 325605-45-6 325605-46-7 325605-47-8 325605-48-9
325605-49-0 325605-50-3 325605-51-4 325605-52-5
RL: PRP (Properties)
(unclaimed **nucleotide** sequence; methods for prepg.
phosphorylated **peptide nucleic acids**
carrying one or more marker, crosslinking, intracellular uptake, or
binding affinity groups)

L49 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:893130 HCAPLUS
DN 134:222969
TI Synthesis and characterization of a tetranucleotide analog containing alternating phosphonate-amide backbone linkages
AU Yu, P.; Wang, W.; Zhang, H.; Yang, X.; Liang, T. C.; Gao, X.
CS Department of Chemistry, University of Houston, Houston, TX, 77204-5641, USA
SO Bioorganic & Medicinal Chemistry (2001), 9(1), 107-119
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
CC 33-10 (Carbohydrates)
Section cross-reference(s): 7, 34
OS CASREACT 134:222969
AB Described herein is the synthesis and characterization of a **tetranucleotide**, 5'-dC-phosphonate-T-amide-T-phosphonate-dC (III), in which the C-T and T-C steps contain a phosphonate backbone bond and T-T is a **peptide nucleic acid** dimer unit (neutral backbone). The 5'- and 3'-OH groups of the tetramer can be further derivatized and, thus, the compd. is a potential building block for longer oligonucleotides which will contain alternating backbone modifications at designated positions. The synthesis involved first the prepn. of two hybrid **peptide**-deoxyribose **dinucleotides**, CT-CO (I) and N-CT (II) (C and T are **nucleobases**; CO and N are carboxylic and amino terminal, resp.); each is linked through a phosphonate linkage. A condensation reaction between the two dimers, followed by deprotection, resulted in the formation of a peptide linkage to give the desired tetramer III. The reaction conditions used are mild to afford products in moderate to excellent yields. The DNA-**PNA**-DNA tetramer, d(CTTC), is a substrate for T4 kinase but fails to give a ligation product, even though NMR shows weak interactions between the tetramer III with its complementary sequence, d(GAAG).
ST **PNA** oligodeoxyribonucleotide phosphonate amide linkage synthesis substrate kinase
IT DNA
**Peptide nucleic acids**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(synthesis and characterization of a **tetranucleotide** analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)
IT 501-53-1, Benzyl chloroformate 15715-58-9, Triethylammonium bicarbonate 128625-52-5
RL: RGT (Reagent); RACT (Reactant or reagent)
(prepn. of)
IT 9015-85-4, DNA ligase 37211-65-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(synthesis and characterization of a tetranucleotide analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)

IT 329326-31-0P
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(synthesis and characterization of a tetranucleotide analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)

IT 56-40-6, Glycine, reactions 107-15-3, Ethylenediamine, reactions 2094-72-6, 1-Adamantanecarbonyl chloride 2857-97-8, Bromotrimethylsilane 5324-30-1 20924-05-4 51549-36-1 51549-37-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and characterization of a tetranucleotide analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)

IT 144912-80-1P 144912-97-0P 210306-41-5P 329326-29-6P 329326-30-9P 329326-32-1P **329326-33-2P** 329326-34-3P 329326-35-4P 329326-36-5P 329326-37-6P 329326-38-7P 329326-39-8P 329326-40-1P 329326-41-2P 329326-42-3P 329326-43-4P 329326-44-5P 329326-45-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and characterization of a tetranucleotide analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)

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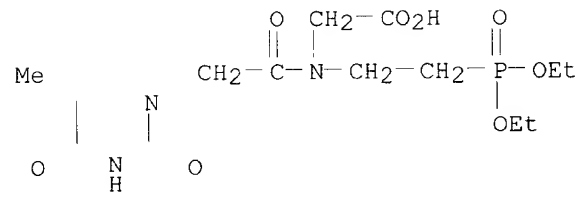
IT **329326-33-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and characterization of a tetranucleotide analog contg. alternating phosphonate-amide backbone linkages as enzyme substrates)

RN 329326-33-2 HCAPLUS
CN Glycine, N-[2-(diethoxyphosphinyl)ethyl]-N-[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl]- (9CI) (CA INDEX NAME)



L49 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:520988 HCAPLUS
DN 129:257138
TI Prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liquid chromatography
AU Hoffmann, Ralf; Bril, Gordon; Otvos, Laszlo
CS The Wistar Institute, Philadelphia, PA, 19104, USA
SO Journal of Chromatography, A (1998), 814(1 + 2), 111-119
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier Science B.V.
DT Journal
LA English
CC 9-3 (Biochemical Methods)
Section cross-reference(s): 3

AB **Peptide nucleic acids** (**PNAs**) are synthetic biopolymers consisting of **nucleobase** side chains attached to an amino Et glycine backbone. At present this family of compds. enjoys a well deserved popularity in biomedical research, due to a no. of favorable biol. and chem. properties of **PNAs** compared to conventional synthetic oligonucleotides. **PNAs** are basically peptides, and are synthesized, purified and analyzed by traditional peptide chem., chromatog. and mass spectrometry techniques. In the current report, we analyzed factors that influence the elution behavior of 29 **PNAs** on reversed-phase high-performance liq. chromatog. using a water-acetonitrile-trifluoroacetic acid gradient elution system on C18 columns. We found that increasing the temp. from 25.degree. to 55.degree. resulted in improved peak shape and resoln. The retention times of the **PNA** analogs were dependent upon the length of the polymers with longer **PNAs** eluting later. Mixts. of **PNAs** with varying length, originating from inefficient monomer couplings during the polymer assembly, could be sepd. by single chromatog. runs. The retention time also depended upon the cytosine, thymine, adenine and guanine content of the polymers. These differences in the contribution to the retention

times could be explained by simple hydrophobicity features of the monomer side chains at pH 1.8. Based on all data, a linear equation was generated which predicted the retention time of any synthetic **PNA** based on compn. and length. Comparison of the predicted and obsd. retention times showed a remarkable reliability of the algorithm.

ST **peptide nucleic acid** reversed phase HPLC

IT Algorithm
Reversed phase HPLC
Temperature
(prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liq. chromatog.)

IT **Peptide nucleic acids**
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liq. chromatog.)

IT 213272-46-9 213272-47-0 213272-48-1 **213272-49-2**
213272-50-5 213272-51-6 213272-52-7 213272-53-8 213272-54-9
213272-55-0 213272-56-1 213395-27-8 213395-29-0 213395-31-4
213395-33-6 213395-34-7 213395-36-9 213395-38-1 213395-40-5
213395-42-7 213395-43-8 213395-45-0 213395-46-1 213395-47-2
213395-48-3 213395-49-4 213395-50-7 213395-51-8 213395-52-9
RL: ANT (Analyte); ANST (Analytical study)
(prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liq. chromatog.)

IT 65-71-4, Thymine 71-30-7, Cytosine 73-24-5, Adenine, properties
73-40-5, Guanine
RL: PRP (Properties)
(prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liq. chromatog.)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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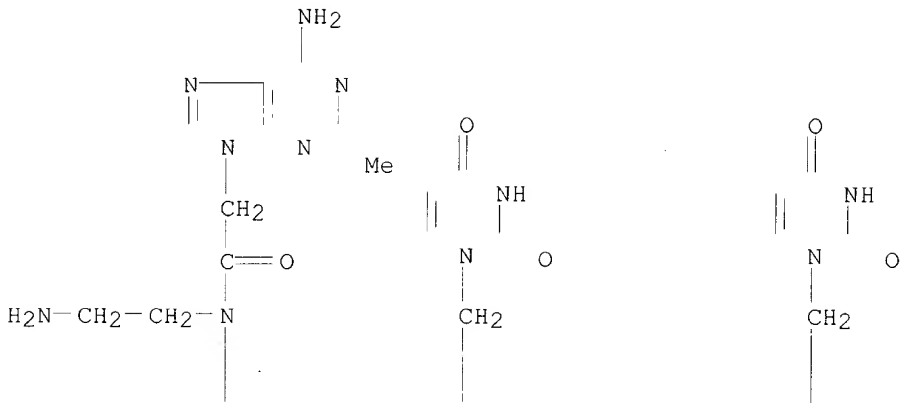
IT **213272-49-2**
RL: ANT (Analyte); ANST (Analytical study)
(prediction of retention times of **peptide nucleic acids** during reversed-phase high-performance liq. chromatog.)

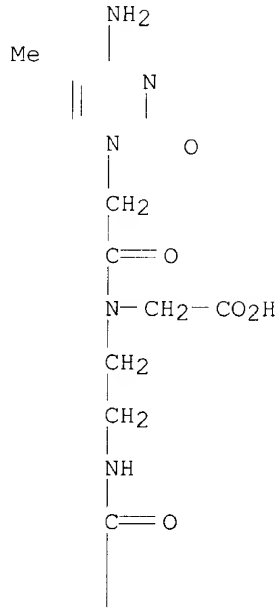
RN 213272-49-2 HCAPLUS

CN Peptide nucleic acid, (H-A-T-U-G-m5C)-OH (9CI) (CA INDEX NAME)

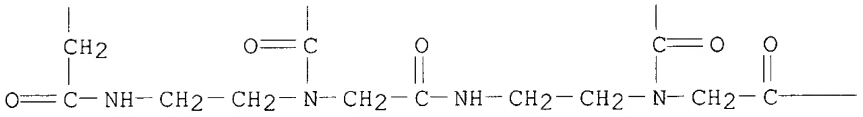
PAGE 1-A



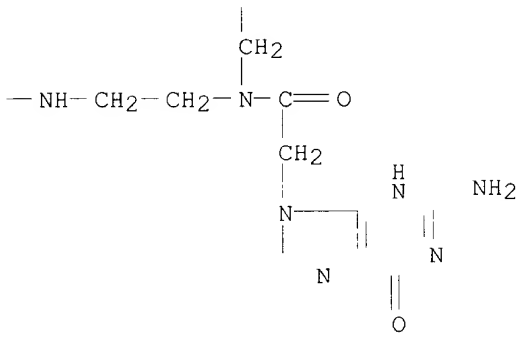
PAGE 1-B



PAGE 2-A



PAGE 2-B



L49 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:356548 HCAPLUS
DN 126:326433
TI a FISH method for detecting and quantifying multiple copies of a repeat sequence in a nucleic acid molecule in a single cell
IN Lansdorp, Peter
PA Lansdorp, Peter, Can.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N
CC 3-1 (Biochemical Genetics)
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9714026 | A2 | 19970417 | WO 1996-CA676 | 19961010 |
| | WO 9714026 | A3 | 19970724 | | |
| | W: CA, JP, US | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | EP 870055 | A2 | 19981014 | EP 1996-932411 | 19961010 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | US 6514693 | B1 | 20030204 | US 1996-730635 | 19961011 |
| | US 2003022204 | A1 | 20030130 | US 2002-132002 | 20020425 |
| PRAI | US 1995-5590P | P | 19951012 | | |
| | US 1995-7616P | P | 19951128 | | |
| | US 1996-730635 | A | 19961011 | | |
| | WO 1996-CA676 | W | 19961010 | | |

AB A hybridization method for detecting or quantifying multiple copies of a repeat sequence in a nucleic acid mol. using a labeled hybridization probe is described. The method is preferably used for quantitating multiple copies of a repeat sequence in a nucleic acid mol., preferably a telomere or centromere repeat sequence. The preferred label is a fluorescent group and quantitation is by quant. fluorimtery. Novel probes for use in the method of the invention and kits are described. Using FITC-labeled

**peptide nucleic acid** probes, telomeres of
sister chromatids showed similar fluorescence, but fluorescence levels depended upon the chromosome. Fluorescence intensity also dropped with the no. of cell divisions that the cell had gone through.

ST repeat DNA detection quantitation; telomere repeat detection quantitation FISH

IT Chemiluminescence spectroscopy
(FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT Repetitive DNA
RL: ANT (Analyte); ANST (Analytical study)
(FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT Centromeres
Telomeres (chromosome)
(detection of repeat sequences at; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT Nucleic acid hybridization
(in situ, fluorescence; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT Nucleic acid hybridization
(in situ; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT **Peptide nucleic acids**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(labeled, hybridization probes for telomere repeat sequences; FISH method for detecting and quantifying multiple copies of repeat sequence in **nucleic acid** mol. in single cell)

IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(labeled; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT Fluorometry
(quant.; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT 120178-12-3, Telomerase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(assay for ligands of, hybridization assay for telomere repeat DNA in; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT 89802-96-0D, oligomers, conjugates with reporter moieties
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(hybridization probe for telomere repears; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT 189444-15-3D, oligomers, conjugates 189444-16-4D, oligomers, conjugates 189444-17-5D, oligomers, conjugates 189444-18-6D, oligomers, conjugates 189444-19-7D, oligomers, conjugates 189444-20-0D, oligomers, conjugates 189444-21-1D, oligomers, conjugates **189444-22-2D**, oligomers, conjugates 189444-23-3D, oligomers, conjugates 189444-24-4D, oligomers, conjugates 189520-39-6D, oligomers, conjugates 189520-40-9D, oligomers, conjugates
RL: ARG (Analytical reagent use); PRP (Properties); ANST (Analytical study); USES (Uses)
(hybridization probe; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

IT 117490-04-7
RL: ANT (Analyte); ANST (Analytical study)
(telomere repeat sequence, detection and quantification of; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

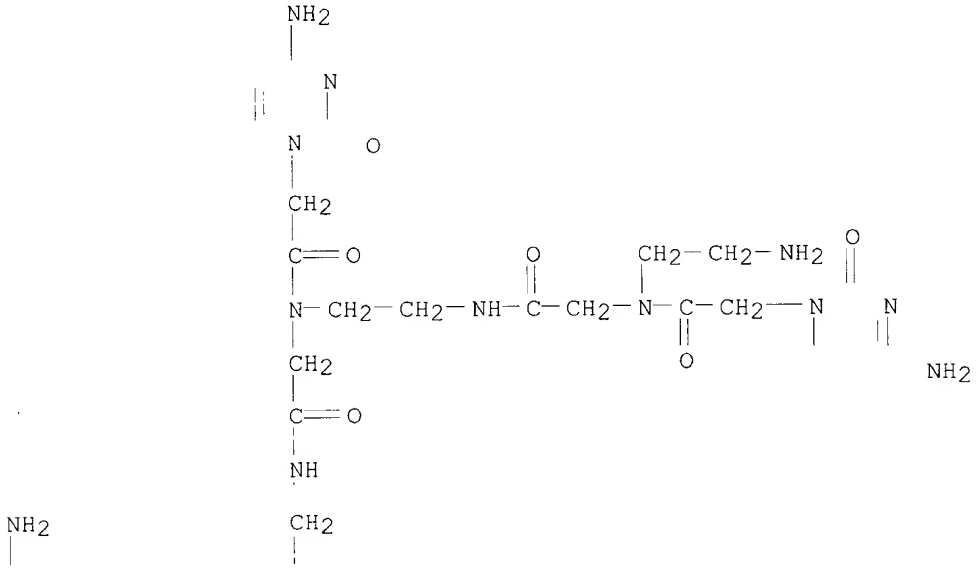
IT **189444-22-2D**, oligomers, conjugates

RL: ARG (Analytical reagent use); PRP (Properties); ANST (Analytical study); USES (Uses)
(hybridization probe; FISH method for detecting and quantifying multiple copies of repeat sequence in nucleic acid mol. in single cell)

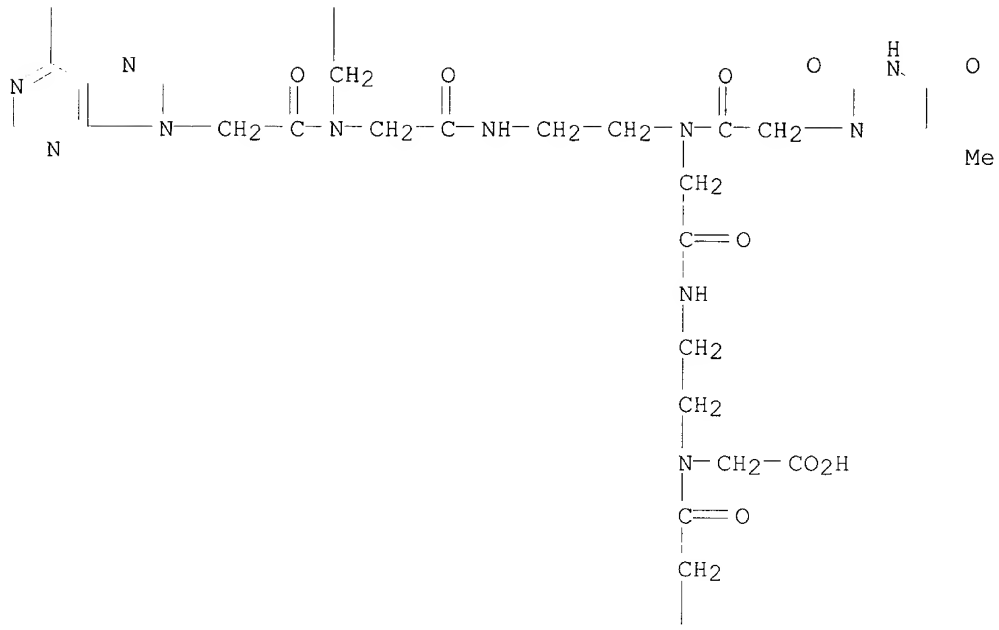
RN 189444-22-2 HCAPLUS

CN Peptide nucleic acid, (H-C-C-A-T-T)-OH (9CI) (CA INDEX NAME)

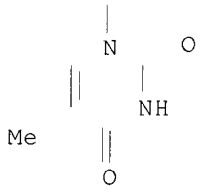
PAGE 1-A



PAGE 2-A



PAGE 3-A



L49 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:88503 HCAPLUS
DN 126:100903
TI Phosphonomonoester nucleic acids, process for their preparation, and their use in molecular biology and as pharmaceuticals
IN Peyman, Anuschirwan; **Uhlmann, Eugen; Breipohl, Gerhard** ; Wallmeier, Holger
PA **Hoechst A.-G., Germany**
SO Can. Pat. Appl., 126 pp.
CODEN: CPXXEB
DT Patent
LA English
IC ICM C12Q001-68
ICS C07K002-00; C07H021-00; A61K048-00; A61K031-70; A61K038-00
CC 6-2 (General Biochemistry)
Section cross-reference(s): 1, 3, 33
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | CA 2171589 | AA | 19960914 | CA 1996-2171589 | 19960312 |
| | DE 19508923 | A1 | 19960919 | DE 1995-19508923 | 19950313 |

DE 19543865 A1 19970605 DE 1995-19543865 19951124
PRAI DE 1995-19508923 A 19950313
DE 1995-19543865 A 19951124
OS CASREACT 126:100903

AB Novel **oligonucleotide** analogs which may be loosely described as phosphonomonoester analogs of **peptide nucleic acids** (PMENA's) and methods for their synthesis are claimed. Particularly preferred PMENA analogs are Q-[OP(:O)(OR)CH2N(COCH2B)CH2CH2]n O-Q' (n=1-25; R=OH, OEt, OPh, etc.; B=natural nucleobase; Q,Q'=H, alkyl, Ph, etc. or an oligonucleotide or modified oligonucleotide). Their application relates to use as inhibitors of gene expression (antisense oligonucleotides, ribozymes, sense oligonucleotides and triplex-forming oligonucleotides), as probes for the detection of nucleic acids and as auxiliaries in mol. biol. PMENA analog H-[OP(:O)(OH)CH2N(COCH2T)CH2CH2]9O P(:O)(OEt)OEt was prepd. and its interaction with (dA)9 examd. by UV spectroscopy and by gel shift anal. The Tm for the PMENA analog-(dA)9 complex was 23.degree..

ST oligonucleotide analog phosphonomonoester synthesis pharmaceutical

IT Oligonucleotides
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(analogs; phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Artery, disease
(coronary, restenosis, prevention of; phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Gene
(expression, inhibition of; phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Antitumor agents
Antiviral agents
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Growth factors, animal
Tumor necrosis factors
RL: MSC (Miscellaneous)
(treatment of diseases involving; phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT Hepatitis B virus
Human herpesvirus 1
Human herpesvirus 2
Human immunodeficiency virus
Influenza virus
Papillomavirus
(treatment of infection by; phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT 185670-74-0P
RL: PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT 50-00-0, Formaldehyde, reactions 100-27-6 107-18-6, 2-Propen-1-ol, reactions 141-43-5, reactions 762-04-9 4712-55-4 14470-28-1 20924-05-4 57260-73-8 78635-98-0 89992-70-1 102774-86-7 172405-10-6 172405-18-4 172405-25-3 185670-94-4
RL: RCT (Reactant); RACT (Reactant or reagent)

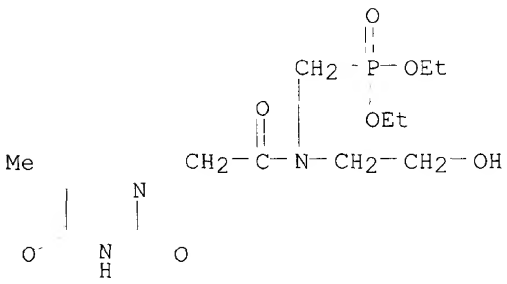
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT 85363-76-4P 105496-31-9P 183057-32-1P 183057-37-6P 183057-48-9P
183057-51-4P 183057-55-8P 183057-59-2P 183057-63-8P 183057-66-1P
183057-69-4P **183057-72-9P** 183057-75-2P 183057-79-6P
183057-82-1P 183057-84-3P 183057-88-7P 183057-91-2P 183057-94-5P
183057-96-7P 183057-99-0P 183058-02-8P 183058-04-0P 183058-06-2P
183058-09-5P 183058-10-8P 183058-11-9P 183058-12-0P 183058-13-1P
183058-14-2P 183058-15-3P 183058-16-4P 183058-18-6P 183058-19-7P
183058-21-1P 183058-22-2P 183058-25-5P 185670-36-4P 185670-58-0P
185670-59-1P 185670-60-4P 185670-61-5P 185670-62-6P 185670-63-7P
185670-64-8P 185670-65-9P 185670-66-0P 185670-67-1P 185670-68-2P
185670-69-3P 185670-70-6P 185670-71-7P 185670-72-8P 185670-76-2P
185670-78-4P 185670-79-5P 185670-80-8P 185670-81-9P 185670-82-0P
185670-84-2P 185670-87-5P 185670-90-0P 185670-92-2P 185670-95-5P
185670-96-6P 185670-97-7P 185670-98-8P 185670-99-9P 185671-00-5P
185671-01-6P 185671-02-7P 185671-03-8P 185830-87-9P 185830-88-0P
185830-89-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

IT **183057-72-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(phosphonomonoester nucleic acids prepn. and use in mol. biol. and as pharmaceuticals)

RN 183057-72-9 HCAPLUS

CN Phosphonic acid, [[[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl](2-hydroxyethyl)amino]methyl]-, diethyl ester (9CI) (CA INDEX NAME)



L49 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:755989 HCAPLUS

DN 126:118140

TI *Phosphonic ester nucleic acids (PHONAs): oligodeoxyribonucleotide analog with an achiral phosphonic acid ester backbone*

AU Peyman, Anusch; **Uhlmann, Eugen**; Wagner, Konrad; Augustin, Sascha; **Breipohl, Gerhard**; **Will, David W.**; Schaefer, Andrea; Wallmeier, Holger

CS **Hoechst AG, Frankfurt, D-65926, Germany**

SO Angewandte Chemie, International Edition in English (1996), 35(22), 2636-2638
CODEN: ACIEAY; ISSN: 0570-0833

PB VCH

DT Journal

LA English

CC 33-9 (Carbohydrates)

Section cross-reference(s): 6

AB The prepn. of polyamide nucleic acid analogs with an achiral and neg. charged backbone to which the nucleobases are attached through carboxymethylene linkers, is reported.

ST oligodeoxyribonucleotide phosphonic ester duplex prepn; PHONA nucleic acid duplex prepn; phosphonic ester nucleic acid duplex prepn; polyamide nucleic acid analog duplex prepn

IT Nucleic acids
Oligodeoxyribonucleotides
RL: SPN (Synthetic preparation); PREP (Preparation)
(phosphonic ester, PHONAs; prepn. of phosphonic ester nucleic acid duplexes)

IT 20924-05-4 77451-51-5 183057-37-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of phosphonic ester nucleic acid duplexes)

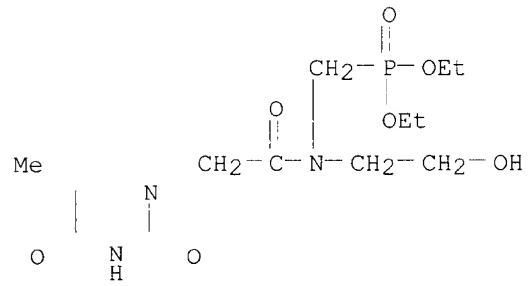
IT 85363-76-4P 183057-48-9P 183057-69-4P **183057-72-9P**
183057-84-3P 183057-87-6P 183058-02-8P 183058-04-0P 183058-10-8P
183058-22-2P 185670-36-4P 185670-58-0P 185670-59-1P 185670-60-4P
185670-64-8P 185670-74-0P 185830-87-9P 186143-34-0P 186143-35-1P
186143-36-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phosphonic ester nucleic acid duplexes)

IT 186272-60-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of phosphonic ester nucleic acid duplexes)

IT **183057-72-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phosphonic ester nucleic acid duplexes)

RN 183057-72-9 HCAPLUS

CN Phosphonic acid, [[[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl](2-hydroxyethyl)amino]methyl]-, diethyl ester (9CI) (CA INDEX NAME)



L49 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:672510 HCAPLUS

DN 125:301493

TI Preparation of nucleic acid phosphonoesters as inhibitors of gene expression.

IN Anuschirwan, Peyman; **Uhlmann, Eugen; Breipohl, Gerhard**; Wallmeier, Holger

PA **Hoechst A.-G., Germany**

SO Ger. Offen., 36 pp.
CODEN: GWXXBX

DT Patent

LA German

IC ICM C07H021-00

ICS C07H001-00; C07F009-6506; A61K031-70
ICA C07F009-38; C07F009-6561; C12N007-06
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 63
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | DE 19508923 | A1 | 19960919 | DE 1995-19508923 | 19950313 |
| | EP 739898 | A2 | 19961030 | EP 1996-103533 | 19960307 |
| | EP 739898 | A3 | 19980916 | | |
| | EP 739898 | B1 | 20010926 | | |
| | R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | AT 206131 | E | 20011015 | AT 1996-103533 | 19960307 |
| | ES 2165446 | T3 | 20020316 | ES 1996-103533 | 19960307 |
| | US 5874553 | A | 19990223 | US 1996-613417 | 19960311 |
| | CA 2171589 | AA | 19960914 | CA 1996-2171589 | 19960312 |
| | NO 9601006 | A | 19960916 | NO 1996-1006 | 19960312 |
| | AU 9648028 | A1 | 19960926 | AU 1996-48028 | 19960312 |
| | AU 706470 | B2 | 19990617 | | |
| | ZA 9601986 | A | 19961121 | ZA 1996-1986 | 19960312 |
| | BR 9600993 | A | 19971230 | BR 1996-993 | 19960312 |
| | JP 08259579 | A2 | 19961008 | JP 1996-84808 | 19960313 |
| | CN 1138588 | A | 19961225 | CN 1996-100508 | 19960313 |
| | CN 1060781 | B | 20010117 | | |
| | US 6127346 | A | 20001003 | US 1998-196132 | 19981120 |
| PRAI | DE 1995-19508923 | A | 19950313 | | |
| | DE 1995-19543865 | A | 19951124 | | |
| | US 1996-613417 | A1 | 19960311 | | |

AB QXP(Z)(:Y)CR5R6L(AB)DGX[P(Z)(:Y)CR5R6L(AB)DGX]nQ1 [n = 0-100; B = H, OH, alkoxy, alkylthio, (un)natural **nucleobase**, reporter ligand, (substituted) alkyl, aryl, aralkyl, heterocyclyl, etc.; AB = amino acid or **peptide** residue; R1 = H, (substituted) alkyl; R5, R6 = H, (substituted) alkyl, aryl, aralkyl, OH, alkoxy, alkylthio; A = bond, CH2, (O-, S-, or NR1-interrupted) (substituted) alkylene; D, G = (substituted) methylene; X, Y = O, S, NR1; Z = OH, alkoxy, alkenyloxy, alkynyloxy, amino, etc.; Q, Q1 = H, conjugate, (modified) **oligonucleotide**], were prepd. as drugs and diagnostic agents (no data). Thus, N-(4-methoxytriphenylmethoxy)ethylaminomethanephosphonic acid di[2-(p-nitrophenyl)ethyl]ester (prepn. given) was stirred with N-ethylmorpholine, HATU, and N6-anisoylcytosine-1-acetic acid in DMF to give a coupling product which was stirred with DBU in MeCN to give N-(N6-anisoylcytosin-1-ylacetyl)-N-(4-methoxytriphenylmethoxy)ethylaminomethanephosphonic acid [2-(p-nitrophenyl)ethyl] monoester.

ST nucleic acid phosphonoester gene expression inhibitor; diagnostic agent nucleic acid phosphonoester; anticancer nucleic acid phosphonoester prepn; restenosis treatment nucleic acid phosphonoester; antiviral nucleic acid phosphonoester

IT Nucleic acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(esters; prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Neoplasm inhibitors
Virucides and Virustats
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Integrins
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(treatment of integrin-influenced disease; prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Diagnosis

(agents, prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Adhesion
(bio-, treatment of cell-cell adhesion-influenced disease; prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Heart, disease
(restenosis, treatment; prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT Lymphokines and Cytokines
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(tumor necrosis factor, treatment of TNF-influenced disease; prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT 183057-48-9P 183057-51-4P 183057-55-8P 183057-63-8P 183057-66-1P
183057-69-4P **183057-72-9P** 183057-75-2P 183057-79-6P
183057-82-1P 183057-84-3P 183057-94-5P 183058-02-8P 183058-06-2P
183058-10-8P 183058-11-9P 183058-12-0P 183058-14-2P 183058-19-7P
183058-22-2P 183058-25-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT 183057-59-2P 183057-88-7P 183057-91-2P 183057-96-7P 183057-99-0P
183058-04-0P 183058-09-5P 183058-13-1P 183058-15-3P 183058-16-4P
183058-18-6P 183058-21-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

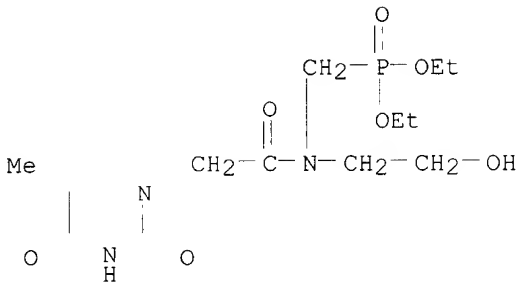
IT 100-27-6 107-18-6, Allyl alcohol, reactions 141-43-5, 2-Aminoethanol, reactions 762-04-9, Diethyl phosphite 1129-37-9, p-Nitrobenzaldoxime 4712-55-4, Diphenyl phosphite 20924-05-4 172405-10-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT 85363-76-4P 105496-31-9P 183057-32-1P 183057-37-6P 183057-42-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

IT **183057-72-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of nucleic acid phosphonoesters as inhibitors of gene expression)

RN 183057-72-9 HCAPLUS

CN Phosphonic acid, [[[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)acetyl](2-hydroxyethyl)amino]methyl]-, diethyl ester (9CI) (CA INDEX NAME)



=> d l50 bib abs retable tot

L50 ANSWER 1 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:805617 HCAPLUS
TI (2'-O-methyl-RNA)-3'-**PNA** chimeras: A new class of mixed backbone oligonucleotide analogues with high binding affinity to RNA
AU Greiner, Beate; **Breipohl, Gerhard**; **Uhlmann, Eugen**
CS Aventis Pharma Deutschland GmbH, Frankfurt a.M., D-65926, Germany
SO Helvetica Chimica Acta (2002), 85(9), 2619-2626
CODEN: HCACAV; ISSN: 0018-019X
PB Verlag Helvetica Chimica Acta
DT Journal
LA English
AB The automated online synthesis of DNA-3'-**PNA** chimeras 1-4 and (2'-O-methyl-RNA)-3'-**PNA** chimeras 5-8 is described, in which the 3'-terminal part of the oligonucleotide is linked to the N-terminal part of the **PNA** via N-(.omega.-hydroxyalkyl)-N-[(thymin-1-yl)acetyl]glycine units (alkyl=Et, Ph, Bu, and pentyl). By means of UV thermal denaturation, the binding affinities of all chimeras were directly compared by detg. their Tm values in the duplex with complementary DNA and RNA. All investigated DNA-3'-**PNA** chimeras and (2'-O-methyl-RNA)-3'-**PNA** chimeras form more-stable duplexes with complementary DNA and RNA than the corresponding unmodified DNA. Interestingly, a N-(3-hydroxypropyl)glycine linker resulted in the highest binding affinity for DNA-3'-**PNA** chimeras, whereas the (2'-O-methyl-RNA)-3'-**PNA** chimeras showed optimal binding with the homologous N-(4-hydroxybutyl)glycine linker. The duplexes of (2'-O-methyl-RNA)-3'-**PNA** chimeras and RNA were significantly more stable than those contg. the corresponding DNA-3'-**PNA** chimeras. Surprisingly, we found that the charged (2'-O-methyl-RNA)-3'-**PNA** chimera with a N-(4-hydroxybutyl)glycine-based unit at the junction to the **PNA** part shows the same binding affinity to RNA as uncharged **PNA**. Potential applications of (2'-O-methyl-RNA)-3'-**PNA** chimeras include their use as antisense agents acting by a RNase-independent mechanism of action, a prerequisite for antisense-oligonucleotide-mediated correction of aberrant splicing of pre-mRNA.

RETABLE

| Referenced Author (RAU) | Year (RPY) | VOL (RVL) | PG (RPG) | Referenced Work (RWK) | Referenced File |
|---|---|---|---|---|---|
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| Breipohl, G | 1996 | | 61 | ` Innovation and Per | HCAPLUS |
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| | | | | | |
|---|---|---|---|---|---|
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| Uhlmann, E | 1996 | 35 | 2632 | Angew Chem, Int Ed | |
| Uhlmann, E | 1998 | 37 | 2796 | Angew Chem, Int Ed | HCAPLUS |
| Uhlmann, E | 1998 | 379 | 1045 | Biol Chem | HCAPLUS |
| Uhlmann, E | 2000 | 3 | 203 | Curr Opin Drug Disco | HCAPLUS |
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| van der Laan, A | 1998 | 8 | 663 | Bioorg Med Chem Lett | HCAPLUS |
| Will, D | 1995 | 51 | 12069 | Tetrahedron | HCAPLUS |

L50 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:780930 HCAPLUS
DN 135:331678
TI Methods for preparing phosphorylated **peptide nucleic acids** carrying one or more marker, crosslinking, intracellular uptake, or binding affinity groups
IN **Uhlmann, Eugen; Breipohl, Gerhard; Will, David William**
PA Aventis Pharma Deutschland G.m.b.H., Germany
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

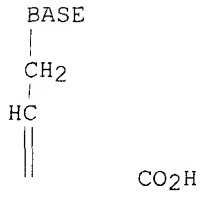
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2001079249 | A2 | 20011025 | WO 2001-EP4027 | 20010407 |
| WO 2001079249 | A3 | 20020328 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10019136 | A1 | 20011031 | DE 2000-10019136 | 20000418 |
| BR 2001010111 | A | 20030211 | BR 2001-10111 | 20010407 |
| EP 1282639 | A2 | 20030212 | EP 2001-919443 | 20010407 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2003022172 | A1 | 20030130 | US 2001-835370 | 20010417 |
| NO 2002004960 | A | 20021112 | NO 2002-4960 | 20021015 |
| PRAI DE 2000-10019136 | A | 20000418 | | |
| WO 2001-EP4027 | W | 20010407 | | |

AB The invention relates to **PNA** derivs. which carry a phosphoryl radical on the N terminus of the **PNA** backbone, for example a phosphate or a substituted phosphoryl radical, substituted phosphoryl derives optionally carrying one or more marker groups or groups for crosslinking or groups which favor intracellular take-up or groups which increase the binding affinity of the **PNA** deriv. to nucleic acids. The invention also relates to a method for producing the aforementioned **PNA** derivs. and to their use as medicaments and diagnostic agents. Thus, several **PNA** chains were prepd.using solid phase peptide synthesis techniques, in which the C-terminal was capped by NH(CH2)6OH and the N-terminal H2N- group was replaced by HO-, and functionalized to H2O3PO- or ROP(O)(OH)O- (R = biotin or fluorescein tag group or alkyl cap). Hybridization tests with complementary DNA or RNA showed increased binding, compared to a normal **PNA** chain N-capped with H3CC(O)- and C-capped with NH(CH2)6OH. In vitro cellular uptake studies were done with fluorescein-tagged **PNA** (no data). In vitro cell proliferation studies were done with a H3C(CH2)15OP(O)(OH)-capped **PNA** using human pre-B leukemia cells or A549-tumor cells

(no data).

L50 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:197663 HCAPLUS
TI Recent progress in the synthesis and cellular uptake of modified oligonucleotides
AU **Uhlmann, Eugen**
CS Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt a. M, 65926, Germany
SO Abstracts of Papers - American Chemical Society (2001), 221st, CARB-010
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB The biol. efficacy of antisense oligonucleotides depends strongly on their cellular uptake and intracellular distribution. In order to improve the uptake characteristics of **oligonucleotides**, several routes have been investigated by us in recent years, including the incorporation of certain **nucleotide** sequence motifs, the covalent attachment of carrier **peptides**, the replacement of the neg. charged phosphodiester linkage by uncharged structural elements, and the conjugation of lipophilic or ionophoric moieties to the oligomers. Depending on the type of modification, other parameters, such as binding affinity, nuclease stability, and the capability of inducing RNase H, were also found to be altered. An overview of various synthetic strategies for the modification of oligonucleotides as well as their impact on the biophys. and biol. properties will be presented.

L50 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:258582 HCAPLUS
DN 133:89771
TI Olefinic **peptide nucleic acids** (OPAs): new aspects of the molecular recognition of DNA by **PNA**
AU Schutz, Rolf; Cantin, Michel; Roberts, Christopher; Greiner, Beate; **Uhlmann, Eugen**; Leumann, Christian
CS Department of Chemistry and Biochemistry, University of Bern, Bern, 3012, Switz.
SO Angewandte Chemie, International Edition (2000), 39(7), 1250-1253
CODEN: ACIEF5; ISSN: 1433-7851
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
GI

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AB In order to study the structural and electrostatic effect of the **PNA** rotameric forms, the authors have synthesized olefinic polyamide nucleic acids (OPAs) in which the central amide functionality was replaced by an isostructural, configurationally stable C-C double bond in either the Z or E configuration (I; BASE = thymidine or adenine), and

used them to prep. (E)- or (Z)-OPA oligomers. A series of mono-substituted **PNAs** and fully-modified (E) and (Z)-OPAs were synthesized and their duplex-forming behavior with DNA studied. Both (E)- and (Z)-OPAs bound to complementary DNA with similar affinities as DNA itself, but in contrast to **PNA**, OPA2/DNA triplexes were not formed, and OPA preferentially bound in the parallel mode to DNA. Results led to the conclusion that amide functionality in the base-linked unit in **PNA** detd. significantly the affinity and preferred strand orientation in **PNA**/DNA duplexes, and seemed to be responsible for the propensity to form PNA2/DNA triplexes; these properties do not depend on the conformational constraints that the amide functionality exerts on the base-linker unit, but rather on its electrostatic properties.

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L50 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:41751 HCAPLUS
DN 132:304723
TI Influence of the type of junction in DNA-3'-**peptide nucleic acid** (**PNA**) chimeras on their binding affinity to DNA and RNA
AU Greiner, Beate; **Breipohl, Gerhard**; **Uhlmann, Eugen**
CS Hoechst Marion Roussel Deutschland GmbH, Chemical Research G 838, Frankfurt, D-65926, Germany
SO Helvetica Chimica Acta (1999), 82(12), 2151-2159
CODEN: HCACAV; ISSN: 0018-019X
PB Verlag Helvetica Chimica Acta
DT Journal
LA English
AB The automated online synthesis of a series of three DNA-3'-**PNA** ( **PNA** = Polyamide Nucleic Acids) chimeras is described, in which the 3'-terminus of the oligonucleotide is linked to the amino terminus of the **PNA** via an N-(2-mercaptoethyl)- (X=S), N-(2-hydroxyethyl)- (X=O), or N-(2-aminoethyl)- (X=NH) N-[(thymin-1-yl)acetyl]glycine unit. In addn., the DNA-3'-**PNA** chimera with no nucleobase at the linking unit was prepd. The binding affinities of all chimeras were directly compared by detg. their Tm values in duplexes with complementary DNA, RNA, or DNA contg. a mismatch or abasic site opposite to the linker unit. We

found that all chimeras in this study which have a nucleobase at the junction were able to form more stable duplexes with complementary DNA and RNA than the corresponding unmodified DNA. The influence of X on duplex stabilization was detd. to be O > S .apprxeq. NH, thus demonstrating the phosphodiester bridge to be the most favored linkage at the DNA/**PNA** junction. The strong duplex-destabilizing effects obsd. when base mismatches or non-basic sites were introduced opposite the nucleobase at the DNA/**PNA** junction, suggest that the base situated at the linking unit contributes significantly to duplex stabilization.

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L50 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:501533 HCAPLUS
DN 132:194633
TI **PNA**/DNA chimeras
AU **Uhlmann, Eugen**; Greiner, Beate; **Breipohl, Gerhard**
CS Hoechst Marion Roussel Deutschland GmbH Chemical Research G 838, Frankfurt am Main, D-65926, Germany
SO Peptide Nucleic Acids (1999), 51-70. Editor(s): Nielsen, Peter E.; Egholm, Michael. Publisher: Horizon Scientific Press, Norfolk, UK. CODEN: 67YLA6
DT Conference
LA English
AB A convenient method for the solid-support synthesis of **PNA**/DNA chimeras is described which makes use of monomethoxytrityl/acyl-protected monomeric building blocks. The acid-labile monomethoxytrityl (Mmt) group is employed for the temporary protection of the amino function of aminoethyl-glycine, while the exocyclic amino functions of the nucleobases are protected with ammonia-cleavable acyl protecting groups. This orthogonal protecting-group strategy is fully compatible with the std. phosphoramidite DNA synthesis method. The resulting **PNA**/DNA chimeras obey the Watson-Crick rules on binding to complementary DNA and RNA. Binding affinity of the **PNA**-DNA chimeras strongly depends on the **PNA**:DNA ratio. The **PNA**/DNA chimeras bind with higher affinity to RNA than to DNA, and the type of linking moiety between **PNA** and DNA could be adjusted to obtain optimal binding affinity. In addn. to their promising binding properties, **PNA**-DNA chimeras can also assume biol. functions, such as a primer function for DNA polymerases. Pure **PNAs** cannot induce RNase H cleavage of target RNA, which often supports the biol. efficacy of antisense agents. In contrast, the DNA-**PNA** chimeras are able to stimulate cleavage of the target RNA by RNase H on formation of a RNA chimera duplex.

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L50 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:310246 HCAPLUS
DN 131:88176
TI Synthesis of a monocharged **peptide nucleic acid** (**PNA**) analog and its recognition as substrate by DNA polymerases
AU Lutz, M. J.; **Will, D. W.**; **Breipohl, G.**; Benner, S. A.; **Uhlmann, E.**
CS Department of Chemistry, Swiss Federal Institute of Technology, Zurich, CH-8092, Switz.
SO Nucleosides & Nucleotides (1999), 18(3), 393-401
CODEN: NUNUD5; ISSN: 0732-8311
PB Marcel Dekker, Inc.
DT Journal
LA English
AB The prepn. of a novel phosphoramidite monomer based on thyminyl acetic acid coupled to the secondary nitrogen of 2-(2-amino-ethyl-amino)ethanol is described. This monomer can be used to attach a deoxy-nucleotide to the carboxy terminus of a **PNA** oligomer by solid-phase synthesis. The resulting **PNA** primer is recognized as a substrate by various DNA polymerases.
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| Will, D | 1995 | 51 | 12069 | Tetrahedron | HCAPLUS |

L50 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:91165 HCAPLUS
TI Minimal modification of antisense oligonucleotides
AU **Uhlmann, E.**
CS Chemical Research, Hoechst Marion Roussel, Frankfurt, 65926, Germany
SO Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), CARB-005 Publisher: American Chemical Society, Washington, D. C.
CODEN: 67GHA6
DT Conference; Meeting Abstract
LA English
AB Uniformly phosphorothioate (PS) modified oligodeoxynucleotides (ODN) are antisense agents of the first generation. Although a no. of PS-ODN are in advanced stages of clin. development and the first antisense drug (Vitravene; Isis Pharmaceuticals) has been approved by the FDA, certain limitations of PS-ODN have emerged. Our approach to overcome these limitations is to reduce the no. of PS linkages within the ODN to a min. which is necessary to stabilize against nucleotlytic degrdn. We have developed a novel protection strategy which is a combination of the end-capping technique and the PS protection of internal pyrimidine positions which are the major sites of endonuclease degrdn. This protection scheme has successfully been used for specific inhibition of expression of various genes. Advantageously, it can also be combined with secondary modifications at the carbohydrate moieties, such as 2'-O-alkyl-modifications, or with partial replacement of the sugar phosphate backbone by 2-aminoethylglycine-based **PNA** units ( **peptide nucleic acid**) leading to DNA-**PNA** chimeras.

L50 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:745539 HCAPLUS
DN 130:66670
TI **PNA**: synthetic polyamide nucleic acids with unusual binding properties
AU **Uhlmann, Eugen**; Peyman, Anusch; **Breipohl, Gerhard**; **Will, David W.**
CS Hoechst Marion Rouseel Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SO Angewandte Chemie, International Edition (1998), 37(20), 2796-2823
CODEN: ACIEF5; ISSN: 1433-7851
PB Wiley-VCH Verlag GmbH
DT Journal; General Review
LA English
AB A review with 160 refs. : since the investigation of oligonucleotides as potential therapeutics that target nucleic acids was initiated, the search for nucleic acid mimetics with improved properties, such as strengthened binding-affinity to complementary nucleic acids, increased biol. stability, and improved cellular uptake, has accelerated rapidly. In 1991 Nielsen et al. first described what is undoubtedly one of the most

interesting of the new derivs., the polyamide or **peptide nucleic acids** (**PNAs**), in which the entire sugar-phosphate backbone is replaced by an N-(2-aminoethyl)glycine polyamide structure. Since even minor structural changes in oligonucleotides, such as the replacement of an oxygen atom by sulfur (phosphorothioates), or by a neutral Me group (Me phosphonates), result in a decrease in binding affinity, it was even more astonishing to find that the drastic structural changes in **PNAs** result in nucleic acid mimetics with higher binding-affinity to complementary DNA and RNA than unmodified oligonucleotides. The remarkable binding properties of **PNAs** have spawned a rapidly expanding new field of research, where the targets are the synthesis of **PNAs** and **PNA** analogs, and their application as therapeutics, DNA diagnostics, and tools in biotechnol. In add., investigation of **PNAs** and **PNA** /DNA chimeras can be used to generate information on the structural and biol. properties of DNA and RNA themselves. Furthermore, they may trigger the generation of new ideas on models for alternative living systems and potential transitions between different genetic systems.

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| Peyman, A | 1996 | 35 | 2636 | Angew Chem Int Ed En | HCAPLUS |
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| Taylor, R | 1997 | 15 | 212 | Nature Genet | HCAPLUS |
| Thiede, C | 1996 | 24 | 983 | Nucleic Acids Res | HCAPLUS |
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| van der Laan, A | 1996 | 37 | 7857 | Tetrahedron Lett | HCAPLUS |
| van der Laan, A | 1997 | 38 | 2249 | Tetrahedron Lett | HCAPLUS |
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| Wenninger, D | 1997 | 16 | 977 | Nucleosides Nucleoti | HCAPLUS |
| Will, D | 1996 | | 65 | Innovation and Persp | HCAPLUS |
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| Xu, Y | 1992 | 57 | 3839 | J Org Chem | HCAPLUS |
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L50 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:667152 HCAPLUS
DN 130:66764
TI DNA-PHONA-**PNA** chimeric molecules: contributions to binding against complementary DNA
AU Peyman, A.; **Uhlmann, E.**; Wagner, K.; Augustin, S.; Weiser, C.; Hein, S.; Langner, D.; **Breipohl, G.**; **Will, D. W.**
CS Hoechst Marion Roussel Deutschland GmbH, Frankfurt, D-65926, Germany
SO Nucleosides & Nucleotides (1998), 17(9-11), 1997-2001
CODEN: NUNUD5; ISSN: 0732-8311
PB Marcel Dekker, Inc.
DT Journal
LA English
AB The synthesis of a DNA-phosphonate **peptide nucleic acid** analog (PHONA)-**peptide nucleic acid** (**PNA**) chimeric mol. using a monomethoxytrityl (Mmt) protection strategy is described. The chimeric oligomer shows duplex binding properties that are comparable to the corresponding **PNA**. Thus, PHONA building blocks can be incorporated into **PNAs** without distortion of the **PNA** structure.

RETABLE

| Referenced Author (RAU) | Year (RPY) | VOL (RVL) | PG (RPG) | Referenced Work (RWK) | Referenced File |
|---|---|---|---|---|---|
| de Mesmaker, A | 1995 | 28 | 366 | Acc Chem Res | |
| Englisch, U | 1991 | 30 | 613 | Angew Chem Int Ed En | |
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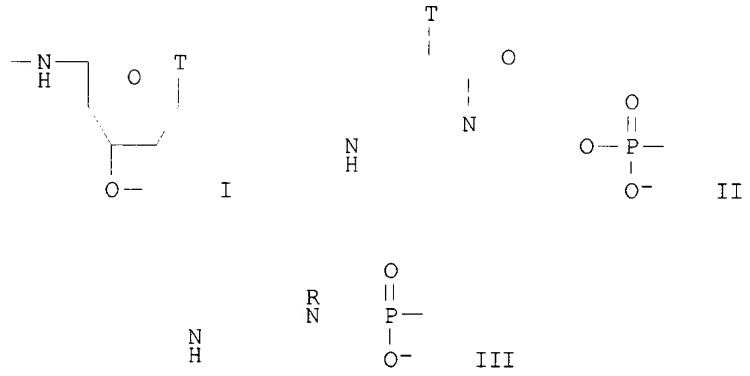
| Peyman, A | 1996 | 35 | 2636 | Angew Chem Int Ed En | HCAPLUS |
| Peyman, A | | | | Angew Chem in the pr | |
| Uhlmann, E | 1996 | 35 | 2632 | Angew Chem Int Ed En | |
| Uhlmann, E | | | | Angew Chem submitted | |
| Uhlmann, E | 1990 | 90 | 543 | Chem Rev | HCAPLUS |
| Uhlmann, E | 1997 | | 64 | Enzyclopedia of Canc | |
| Will, D | 1995 | 51 | 12069 | Tetrahedron | HCAPLUS |

L50 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:618936 HCAPLUS
DN 129:227036
TI **Peptide nucleic acids** (**PNA**) and **PNA**-DNA chimeras. From high binding affinity towards biological function
AU **Uhlmann, Eugen**
CS Hoechst Marion Roussel Deutschland G.m.b.H., Frankfurt/Main, D-65926, Germany
SO Biological Chemistry (1998), 379(8/9), 1045-1052
CODEN: BICHF3; ISSN: 1431-6730
PB Walter de Gruyter & Co.
DT Journal; General Review
LA English
AB A review is given with 45 refs. Oligonucleotide analogs are of major interest as tools in mol. biol., as diagnostics, and as potential pharmaceuticals which bind in a predictable way to certain nucleic acid target sequences, aiming at the inhibition of expression of disease-causing genes. One of the most promising **nucleic acid** mimetics are the **peptide**- or polyamide-**nucleic acids** (**PNA**) which bind with higher affinity to DNA and RNA than natural **oligonucleotides**. In these non-ionic **PNAs**, the entire sugar-phosphate backbone is replaced

by an N-amino-ethylglycine-based polyamide structure. A unique property of **PNA** is its ability to displace one strand of a DNA double-helix. This strand displacement process, which is inefficient with DNA, is supported by the formation of an unusually stable internal ( **PNA**), DNA triple helix. The combination of **PNA** and DNA in 1 mol. results in **PNA**/DNA chimeras with new properties. They show improved aq. soly. compared to pure **PNAs** due to their partially neg. charged structure. The cellular uptake of the chimeras is better than of pure **PNAs**. In contrast to **PNA**, the chimeras bind exclusively in the antiparallel orientation under physiol. conditions. The binding affinity is generally stronger when the **PNA**/DNA chimeras are hybridized to RNA than to DNA, whereby the strength of binding strongly depends on the **PNA**: DNA ratio. **PNA**/DNA chimeras are recognized as substrates by various nucleic acid processing enzymes, and consequently can also assume biol. functions, such as a primer function for DNA polymerases. Pure **PNA** cannot induce RNase H cleavage of target RNA, which is believed to support the biol. efficacy of antisense agents. DNA-**PNA** chimeras are able to stimulate cleavage of the target RNA by RNase H upon formation of an RNA chimera duplex.

L50 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:220217 HCAPLUS
DN 128:321903
TI Optimization of the binding properties of **PNA**-(5')-DNA chimerae
AU van der Laan, A. C.; Havenaar, P.; Oosting, R. S.; Kuyl-Yeheskiely, E.; **Uhlmann, E.**; van Boom, J. H.
CS Gorlaeus Lab., Leiden Inst. of Chemistry, Leiden, 2300 RA, Neth.
SO Bioorganic & Medicinal Chemistry Letters (1998), 8(6), 663-668
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
GI



AB The synthesis and evaluation of **PNA**-(5')-DNA chimera contg. either a 5'-amide (i.e. I; T = thymin-1-yl), a 5'-phosphodiester (i.e. II)

or 5'-phosphonate linkages (i.e. III; R = H, thymin-1-ylacetyl) at the junction site are described. The 5'-linkages were installed using protected phosphoramidite and phosphonate building blocks. It is shown that **PNA-**(5')-DNA of types I, II, and III (R = thymin-1-ylacetyl) have a higher binding affinity with complementary RNA than native DNA, and that the antisense activity is mainly due to RNase H.

RETABLE

| Referenced Author (RAU) | Year (RPY) | VOL (RVL) | PG (RPG) | Referenced Work (RWK) | Referenced File |
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| Dangles, O | 1987 | 52 | 4984 | J Org Chem | HCAPLUS |
| Egholm, M | 1992 | 114 | 1895 | J Am Chem Soc | HCAPLUS |
| Eriksson, M | 1996 | 3 | 410 | Nature Struct Biolog | HCAPLUS |
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| Orum, H | 1995 | 19 | 472 | BioTechniques | MEDLINE |
| Smith, L | 1987 | 155 | 260 | Methods in Enzymolog | HCAPLUS |
| Uhlmann, E | 1996 | 35 | 2632 | Angew Chem Int Ed En | |
| van der Laan, A | 1996 | 37 | 7857 | Tetrahedron Lett | HCAPLUS |
| van der Laan, A | 1997 | 38 | 2249 | Tetrahedron Lett | HCAPLUS |
| Will, D | 1995 | 51 | 12069 | Tetrahedron | HCAPLUS |

L50 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:186571 HCAPLUS
DN 128:240314
TI A **nucleic acid** amplification method using **peptide nucleic acids** as primers for thermostable DNA polymerases
IN **Uhlmann, Eugen**; **Breipohl, Gerhard**; Benner, Steven; Lutz, Michael
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 829542 | A1 | 19980318 | EP 1997-115521 | 19970908 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| DE 19637339 | A1 | 19980319 | DE 1996-19637339 | 19960913 |
| US 6063571 | A | 20000516 | US 1997-927274 | 19970911 |
| CA 2215489 | AA | 19980313 | CA 1997-2215489 | 19970912 |
| JP 10099088 | A2 | 19980421 | JP 1997-250443 | 19970916 |
| PRAI DE 1996-19637339 | | 19960913 | | |

AB A method of using **peptide nucleic acids** (**PNAs**) as primers for DNA amplification with thermostable DNA polymerases, i.e. in PCR, is described. The only modification to the **PNAs** that is essential is the introduction of 1-3 3'-terminal deoxynucleotides with a free 3'-hydroxyl group. Methods for the synthesis of deoxynucleotide-terminated primers are also given.

RETABLE

| Referenced Author (RAU) | Year (RPY) | VOL (RVL) | PG (RPG) | Referenced Work (RWK) | Referenced File |
|---|---|---|---|---|---|
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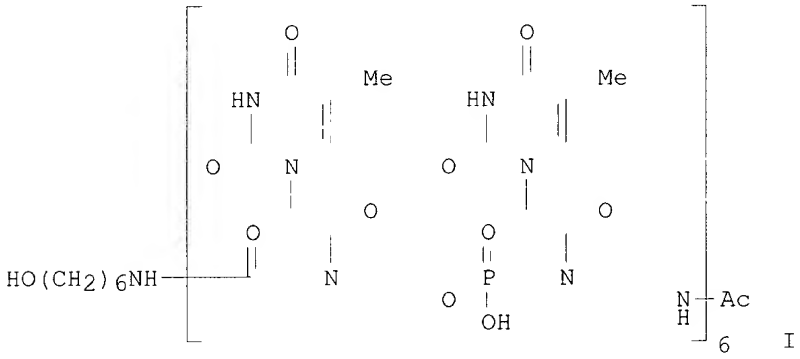
Stratagene Inc | | | |WO 9516028 A |HCAPLUS

L50 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:70167 HCAPLUS
DN 128:167687
TI PHONA - **PNA** co-oligomers: nucleic acid mimetics with interesting properties
AU Peyman, Anusch; **Uhlmann, Eugen**; Wagner, Konrad; Augustin, Sascha; Weiser, Caroline; **Will, David W.**; **Breipohl, Gerhard**
CS Hoechst Marion Roussel Deutschland GmbH, Frankfurt, D-65926, Germany
SO Angewandte Chemie, International Edition in English (1998), Volume Date 1997, 36(24), 2809-2812
CODEN: ACIEAY; ISSN: 0570-0833
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
GI




AB Alternating title co-oligomer I contg. **peptide nucleic acid** (**PNA**) and (aminomethyl)phosphonic acid backbones was prepd. and melting temps. (Tm) of complexes with completely or partially complementary DNA measured. The binding properties of I with complementary DNA are very similar to those of **PNAs**, but the co-oligomer I has a much better water soly.

RETABLE

| Referenced Author (RAU) | Year (RPY) | VOL (RVL) | PG (RPG) | Referenced Work (RWK) | Referenced File |
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| Carpino, L | 1993 | 115 | 4397 | J Am Chem Soc | HCAPLUS |
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| Egholm, M | 1992 | 114 | 9677 | J Am Chem Soc | HCAPLUS |
| Englisch, U | 1991 | 103 | 629 | Angew Chem | HCAPLUS |
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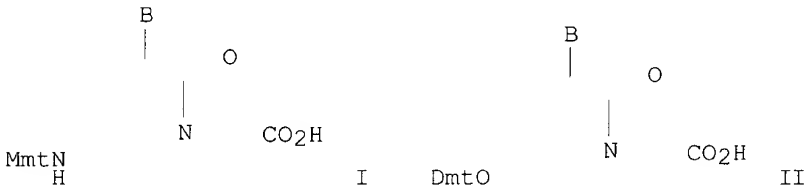
| Peyman, A | 1996 | | | EP 0739898 A2 | HCAPLUS |
| Peyman, A | 1996 | 108 | 2797 | Angew Chem | |
| Peyman, A | 1996 | 35 | 2636 | Angew Chem Int Ed En | HCAPLUS |
| Reese, C | 1978 | 34 | 3143 | Tetrahedron | HCAPLUS |
| Shikata, H | 1995 | 125 | 421 | J Lab Clin Med | HCAPLUS |
| Trapane, T | 1996 | 35 | 5495 | Biochemistry | HCAPLUS |
| Uhlmann, E | 1996 | 108 | 2793 | Angew Chem | |
| Uhlmann, E | 1996 | 35 | 2632 | Angew Chem Int Ed En | |
| Uhlmann, E | 1990 | 90 | 543 | Chem Rev | HCAPLUS |
| Uhlmann, E | 1997 | | 64 | Encyclopedia of Canc | |
| Uhlmann, E | 1981 | 64 | 1688 | Helv Chim Acta | HCAPLUS |
| Uhlmann, E | 1993 | | 355 | Methods in Molecular | HCAPLUS |
| van der Laan, A | 1995 | 114 | 295 | Recl Trav Chim Pays- | HCAPLUS |
| van der Laan, A | 1996 | 37 | 7857 | Tetrahedron Lett | HCAPLUS |
| Will, D | 1995 | 51 | 12069 | Tetrahedron | HCAPLUS |

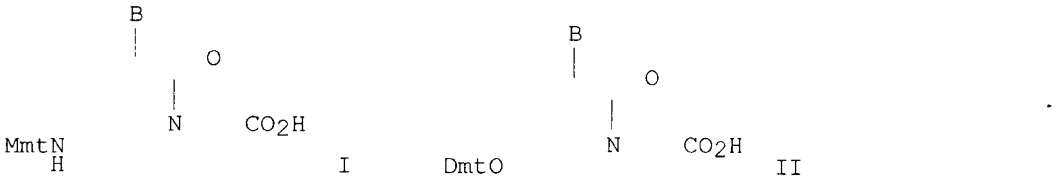
L50 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:758327 HCAPLUS
Correction of: 1997:714702
DN 127:346655
Correction of: 127:319261
TI Novel synthetic routes to **PNA** monomers and **PNA**-DNA linker molecules
AU **Breipohl, Gerhard; Will, David W.**; Peyman, Anusch; **Uhlmann, Eugen**
CS Hoechst Marion Roussel Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SO Tetrahedron (1997), 53(43), 14671-14686
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier
DT Journal
LA English
GI




AB Novel methods for the prepn. of monomethoxytrityl (Mmt)-protected aminoethylglycine building blocks [I; B = 1-thyminyl, N4-(4-methoxybenzoyl)-1-cytosinyl, N6-(4-methoxybenzoyl)-9-adeninyl, N2-acetyl-O6-diphenylcarbamoyl-9-guaninyl, N2-isobutyryl-9-guaninyl] and dimethoxytrityl (Dmt)-protected hydroxyethylglycine derivs. II, useful for the synthesis of polyamide nucleic acids (**PNAs**) and **PNA** /DNA chimeras, are described. The protecting group strategy employed for **PNA** monomer synthesis produces intermediates that are easily isolated, minimizes chromatog. purifn., and is suitable for large-scale monomer synthesis.

L50 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:714702 HCAPLUS
DN 127:319261
TI Novel synthetic routes to **PNA** monomers and **PNA**-DNA linker molecules

AU **Breipohl, Gerhard; Will, David W.**; Peyman, Anusch; Uhimann, Eugen
CS Hoechst Marion Roussel Deutschland GmbH, Frankfurt am Main, D-65926, Germany
SO Tetrahedron (1997), 53(43), 14671-14686
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier
DT Journal
LA English
GI




AB Novel methods for the prepn. of monomethoxytrityl (Mmt)-protected aminoethylglycine building blocks I [B = 1-thyminyl, N4-(4-methoxybenzoyl)-1-cytosinyl, N6-(4-methoxybenzoyl)-9-adeninyl, N2-acetyl-O6-diphenylcarbamoyl-9-guaninyl, N2-isobutyryl-9-guaninyl] and dimethoxytrityl (Dmt)-protected hydroxyethylglycine derivs. II, useful for the synthesis of polyamide nucleic acids (**PNAs**) and **PNA** /DNA chimeras are described. The protecting group strategy employed for **PNA** monomer synthesis produces easily isolable intermediates, minimizes chromatog. purifn., and is suitable for large-scale monomer synthesis.

L50 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:591221 HCAPLUS
DN 127:262910
TI Synthesis of polyamide nucleic acids (**PNAs**), **PNA** /DNA-chimeras and phosphonic ester nucleic acids (PHONAs)
AU **Uhlmann, E.**; **Will, D. W.**; **Breipohl, G.**; Peyman, A.; Langner, D.; Knolle, J.; O'Malley, G.
CS Central Pharma Res., Hoechst AG, Frankfurt, D-65926, Germany
SO Nucleosides & Nucleotides (1997), 16(5 & 6), 603-608
CODEN: NUNUD5; ISSN: 0732-8311
PB Dekker
DT Journal; General Review
LA English
AB A review with 18 refs. on methods for the prepn. of polyamide nucleic acids (**PNAs**) and derivs. thereof by different synthetic routes is described. The first strategy makes use of 9-Fluorenylmethoxycarbonyl (Fmoc)/monomethoxytrityl (Mmt) protected building blocks, whereas the second approach involves the use of Mmt/acyl protected monomers, which allows the prepn. of **PNA**/DNA chimera. Addnl., a block coupling strategy is presented for the synthesis of novel phosphonic ester nucleic acids (PHONAs).

L50 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:412349 HCAPLUS
DN 127:66087
TI Solid-phase synthesis of **PNA**-DNA chimeric oligomers
AU **Will, D.W.**; **Breipohl, G.**; Langner, D.; **Uhlmann, E.**
CS Hoechst AG, Allgemeine Pharma Forschung G838, Frankfurt am Main, D-65926, Germany

SO Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemical Diversity, Collected Papers, International Symposium, 4th, Edinburgh, Sept. 12-16, 1995 (1996), Meeting Date 1995, 65-68. Editor(s): Epton, Roger. Publisher: Mayflower Scientific, Birmingham, UK. CODEN: 64ONA9
DT Conference
LA English
AB A symposium on **PNA**-DNA chimeric oligomers have been prepd. using automated solid-phase prepn. A novel Mmt protecting-group strategy for the **PNA** part of the mol. was employed which allowed the use of std. DNA synthesis and deprotection chem.

L50 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:412348 HCAPLUS
DN 127:66086
TI Synthesis of polyamide nucleic acids using a new protection scheme which is fully compatible with oligonucleotide synthesis
AU **Breipohl, G.**; **Will, D.W.**; Langner, D.; Knolle, J.; **Uhlmann, E.**
CS Hoechst AG, Allgemeine Pharma Forschung G838, Frankfurt am Main, D-65926, Germany
SO Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemical Diversity, Collected Papers, International Symposium, 4th, Edinburgh, Sept. 12-16, 1995 (1996), Meeting Date 1995, 61-64. Editor(s): Epton, Roger. Publisher: Mayflower Scientific, Birmingham, UK. CODEN: 64ONA9
DT Conference
LA English
AB A symposium on the prepn. of novel monomethoxytrityl (Mmt) protected monomers for the prepn. of polyamide nucleic acids (**PNAs**) is described. Use of the acid-labile Mmt group as temporary protection for the primary amino function of aminoethylglycine in combination with base-labile acyl-type protecting groups for the nucleobases allow a synthetic strategy similar to std. oligo-nucleotide synthesis conditions. **PNAs** of mixed base sequence have been synthesized with this method.

L50 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:380031 HCAPLUS
Correction of: 1996:755988
DN 127:2136
Correction of: 126:141081
TI Synthesis and properties of **PNA**/DNA chimeras
AU **Uhlmann, Eugen**; **Will, David W.**; **Breipohl, Gerhard**; Langner, Dietrich; Ryte, Antonina
CS Hoechst AG, Frankfurt/Main, D-65926, Germany
SO Angewandte Chemie, International Edition in English (1996), 35(22), 2632-2635
CODEN: ACIEAY; ISSN: 0570-0833
PB VCH
DT Journal
LA English
AB We have developed a generally applicable method for the automated synthesis of DNA/**PNA** chimeras. This method is fully compatible with std. DNA synthesis methods and requires no addnl. deprotection steps at the end of oligomer synthesis. The binding affinity of DNA-**PNA** chimeras is higher than that of the comparable DNA-phosphorothioate chimeras or natural oligonucleotides. Unlike pure **PNAs**, the DNA-**PNA** chimeras investigated bind only in the antiparallel orientation to their complementary nucleic acids under physiol conditions.

L50 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:283607 HCAPLUS
DN 126:264359
TI Preparation of ethylglycine derivatives
IN **Breipohl, Gerhard; Uhlmann, Eugen; Will, David William**
PA Hoechst A.-G., Germany
SO Ger. Offen., 14 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | DE 19532553 | A1 | 19970306 | DE 1995-19532553 | 19950904 |
| | EP 761681 | A2 | 19970312 | EP 1996-113530 | 19960822 |
| | EP 761681 | A3 | 19970709 | | |
| | EP 761681 | B1 | 20020313 | | |
| | R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | AT 214398 | E | 20020315 | AT 1996-113530 | 19960822 |
| | ES 2173230 | T3 | 20021016 | ES 1996-113530 | 19960822 |
| | AU 9664408 | A1 | 19970306 | AU 1996-64408 | 19960902 |
| | AU 708034 | B2 | 19990729 | | |
| | CA 2184681 | AA | 19970305 | CA 1996-2184681 | 19960903 |
| | NO 9603677 | A | 19970305 | NO 1996-3677 | 19960903 |
| | JP 09124572 | A2 | 19970513 | JP 1996-232692 | 19960903 |
| | US 5817811 | A | 19981006 | US 1996-707149 | 19960903 |
| PRAI | DE 1995-19532553 | A | 19950904 | | |

OS MARPAT 126:264359
AB N-ethylglycine derivs. PG-X-CH2CH2N(COCH2B1)CH2CO2H (PG is a urethane- or trityl-type amino protecting group which is cleavable by weak acid; X = NH or O; B1 = nucleotide base in which exocyclic amino or hydroxy groups are protected), useful in **PNA** or **PNA**/DNA hybrid prepn., were prepd. Thus, 2-aminoethanol was condensed with bromoacetic acid t-Bu ester, then with thyminylacetic acid, the product deesterified, and the acid treated with DMT-Cl to give a protected **PNA** monomer.

L50 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:224058 HCAPLUS
DN 126:274010
TI Recognition of Uncharged Polyamide-Linked Nucleic Acid Analogs by DNA Polymerases and Reverse Transcriptases
AU Lutz, Michael J.; Benner, Steven A.; Hein, Silvia; **Breipohl, Gerhard; Uhlmann, Eugen**
CS Department of Chemistry, Swiss Federal Institute of Technology, Zurich, CH-8092, Switz.
SO Journal of the American Chemical Society (1997), 119(13), 3177-3178
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Polyamide-linked nucleic acid (**PNAs**) are DNA mimics in which the deoxyribose phosphate backbone is replaced by uncharged N-(2-aminoethyl)glycine units. Here, the authors report that several DNA polymerases and reverse transcriptases are able to elongate a **PNA** primer with a nucleophilic 3'-hydroxyl group, despite the fact that no phosphate residues are present in the **PNA** primer to interact with the polymerase. Enzymic synthesis of **PNA**-DNA chimeras might have implications for the use of modified **PNAs** in advanced diagnostic systems, allowing facilitated screening for genetic mutations, and as tools for studying structure-function relationships in enzymes that process nucleic acids. These results are also interesting in the light of models for the origin of life that propose an evolutionary linkage between

a **PNA**-like and a DNA-protein world.

L50 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:755988 HCAPLUS
DN 126:141081
TI Synthesis and properties of **PNA**/DNA chimeras
AU **Uhlmann, Eugen; Will, David W.; Breiphohl, Gerhard**; Langner, Dietrich; Ryte, Antonina
CS Hoechst AG, Frankfurt/Main, D-65926, Germany
SO Angewandte Chemie, International Edition in English (1996), 35(22), 2632-2635
CODEN: ACIEAY; ISSN: 0570-0833
PB VCH
DT Journal
LA English
AB We have developed a generally applicable method for the automated synthesis of DNA/**PNA** chimeras. This method is fully compatible with std. DNA synthesis methods and requires no addnl. deprotection steps at the end of oligomer synthesis. The binding affinity of DNA-**PNA** chimeras is higher than that of the comparable DNA-phosphorothioate chimeras or natural oligonucleotides. Unlike pure **PNAs**, the DNA-**PNA** chimeras investigated bind only in the antiparallel orientation to their complementary nucleic acids under physiol. conditions.

L50 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:508642 HCAPLUS
Correction of: 1996:190218
DN 125:168639
Correction of: 124:344062
TI Synthesis of polyamide nucleic acids (**PNAs**) using a novel Fmoc/Mmt protecting-group combination
AU **Breipohl, G.**; Knolle, J.; Langner, D.; O'Malley, G.; **Uhlmann, E.**
CS Central Pharma Res., Hoechst AG, Frankfurt, 65926, Germany
SO Bioorganic & Medicinal Chemistry Letters (1996), 6(6), 665-670
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
AB The prepn. of 9-fluorenylmethoxycarbonyl (Fmoc) protected building blocks for the synthesis of polyamide nucleic acids (**PNAs**) is described. Use of 4-methoxyphenyldiphenylmethyl (Mmt)-protecting groups for the exocyclic amino function of the nucleobases enhances the soly. of the monomers and allows final deprotection by mild acid treatment. The novel synthetic route is exemplified by the synthesis of heptameric and octameric **PNAs**.

L50 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:190218 HCAPLUS
DN 124:344062
TI Synthesis of polyamide nucleic acids (**PNAs**) using a novel Fmoc/Mmt protecting-group combination
AU Breipohol, G.; Knolle, J.; Langner, D.; O, Malley, G.; **Uhlmann, E.**
CS Central Pharma Research, Hoechst AG, Frankfurt, 65926, Germany
SO Bioorganic & Medicinal Chemistry Letters (1996), 6(6), 665-70
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
AB The prepn. of 9-fluorenylmethoxycarbonyl (Fmoc) protected building blocks for the synthesis of polyamide nucleic acids (**PNAs**) is described. Use of 4-methoxyphenyldiphenylmethyl (Mmt)-protecting groups

for the exocyclic amino function of the nucleobases enhances the soly. of the monomers and allows final deprotection by mild acid treatment. The novel synthetic route is exemplified by the synthesis of heptameric and octameric **PNAs.**

L50 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:47656 HCAPLUS
DN 124:199545
TI Activation of c-Fos contributes to amyloid .beta.-peptide-induced neurotoxicity
AU Gillardon, F.; Skutella, T.; **Uhlmann, E.**; Holsboer, F.; Zimmermann, M.; Behl, C.
CS II. Physiologisches Institut der Universitaet Heidelberg, INF 326, Heidelberg, 69120, Germany
SO Brain Research (1996), 706(1), 169-72
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English
AB Amyloid .beta. peptide, a major component of Alzheimer's disease plaques, is directly toxic to various neuronal cell lines and primary neurons in culture. The mechanism underlying A.beta. neurotoxicity may include an increase in intracellular calcium and reactive oxygen species. In the present study, exposure of a mouse hippocampal cell line (HT-22) to the 25-35 peptide fragment of A.beta. (10 .mu.M) caused a rapid and sustained increase in nuclear c-Fos immunoreactivity. Inhibition of A.beta.-mediated c-Fos activation by c-fos antisense oligodeoxynucleotides (5 .mu.M) significantly protected against A.beta. toxicity as assessed by MTT assay. The signal transduction pathway for c-fos induction remains speculative, however, there seems to be a causal relationship between c-Fos transcription factor and A.beta. toxicity.

L50 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:994444 HCAPLUS
DN 124:202955
TI Preparation of polyamide-oligonucleotide derivatives as drugs, gene probes, and primers.
IN **Uhlmann, Eugen; Breipohl, Gerhard**
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 51 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 672677 | A2 | 19950920 | EP 1995-103332 | 19950308 |
| | EP 672677 | A3 | 19960117 | | |
| | EP 672677 | B1 | 20020703 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | DE 4408528 | A1 | 19950928 | DE 1994-4408528 | 19940314 |
| | EP 1113021 | A2 | 20010704 | EP 2001-104012 | 19950308 |
| | EP 1113021 | A3 | 20010711 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE | | | | |
| | AT 220070 | E | 20020715 | AT 1995-103332 | 19950308 |
| | ES 2179080 | T3 | 20030116 | ES 1995-103332 | 19950308 |
| | FI 9501132 | A | 19950915 | FI 1995-1132 | 19950310 |
| | AU 9514798 | A1 | 19950921 | AU 1995-14798 | 19950310 |
| | AU 698210 | B2 | 19981029 | | |
| | CA 2144475 | AA | 19950915 | CA 1995-2144475 | 19950313 |
| | NO 9500955 | A | 19950915 | NO 1995-955 | 19950313 |
| | CN 1112126 | A | 19951122 | CN 1995-102946 | 19950313 |
| | JP 07278179 | A2 | 19951024 | JP 1995-54644 | 19950314 |

PRAI DE 1994-4408528 A 19940314
EP 1995-103332 A3 19950308
AB F[(QB)q(Q1B)r(Q2B)s(Q3B)t]xF1 [q, r, s, t = 0, 1; X = 1-20; Q, Q2 = nucleic acid (deriv.); Q1, Q3 = polyamide residue contg. .gtoreq.1 nucleic acid base except thymine; B = covalent bond, org. residue contg. .gtoreq.1 of C, N, O, S; F, F1 = end groups which may be bound to each other], were prepd. Title compds. show increased cellular uptake, improved nuclease stability, and are not cytotoxic; they are claimed for use as drugs and gene probes.

L50 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:994428 HCAPLUS
DN 124:87805
TI **Peptide nucleic acid** synthesis using an amino protecting group which is labile to weak acids.
IN **Breipohl, Gerhard Dr; Uhlmann, Eugen Dr**
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 672700 | A1 | 19950920 | EP 1995-103318 | 19950308 |
| EP 672700 | B1 | 19990602 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| DE 4408531 | A1 | 19950928 | DE 1994-4408531 | 19940314 |
| AT 180805 | E | 19990615 | AT 1995-103318 | 19950308 |
| ES 2132450 | T3 | 19990816 | ES 1995-103318 | 19950308 |
| FI 9501130 | A | 19950915 | FI 1995-1130 | 19950310 |
| AU 9514801 | A1 | 19950921 | AU 1995-14801 | 19950310 |
| AU 695931 | B2 | 19980827 | | |
| CA 2144477 | AA | 19950915 | CA 1995-2144477 | 19950313 |
| NO 9500957 | A | 19950915 | NO 1995-957 | 19950313 |
| JP 07285989 | A2 | 19951031 | JP 1995-54642 | 19950314 |
| US 6046306 | A | 20000404 | US 1997-927178 | 19970911 |

PRAI DE 1994-4408531 19940314
US 1995-402385 19950313
AB RAk(XB1)nQ1Q1 [XB = NH(CH2)fCH2N(COCH2B)(CH2)fO, NHCH[(CH2)fB]CONHCH2CO, NHCH[(CH2)fB](CH2)3CO, etc.; f = 1-4; k, l = 0-10; A, Q = amino acid residue; B = (un)natural nucleic acid base or prodrug or replacement forms thereof; Q1 = OH, amino], were prepd. by solid phase synthesis. Thus, H-[Aeg(T)]3hex [Aeg(T) = N-(2-aminoethyl)-N-[(1-thyminyl)acetyl]glycyl, hex = HN(CH2)6OH] was prepd. on hex-succ-tentagel (succ = succinoyl) (prepn. given) on a DNA synthesizer.

L50 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:994427 HCAPLUS
DN 124:87804
TI **Peptide nucleic acid** synthesis using a base labile amino protecting group.
IN **Breipohl, Gerhard Dr; Uhlmann, Eugen Dr**; Knolle, Jochen Dr
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 672701 | A1 | 19950920 | EP 1995-103319 | 19950308 |

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|---|---|---|---|---|---|
| | EP 672701 | B1 | 19990728 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | DE 4408533 | A1 | 19950928 | DE 1994-4408533 | 19940314 |
| | AT 182602 | E | 19990815 | AT 1995-103319 | 19950308 |
| | ES 2136755 | T3 | 19991201 | ES 1995-103319 | 19950308 |
| | FI 9501129 | A | 19950915 | FI 1995-1129 | 19950310 |
| | AU 9514800 | A1 | 19950921 | AU 1995-14800 | 19950310 |
| | AU 683714 | B2 | 19971120 | | |
| | CA 2144473 | AA | 19950915 | CA 1995-2144473 | 19950313 |
| | NO 9500958 | A | 19950915 | NO 1995-958 | 19950313 |
| | JP 07291909 | A2 | 19951107 | JP 1995-54641 | 19950314 |
| | US 6121418 | A | 20000919 | US 1997-967197 | 19971029 |
| | US 6316595 | B1 | 20011113 | US 2000-495457 | 20000201 |
| PRAI | DE 1994-4408533 | A | 19940314 | | |
| | US 1995-402844 | B1 | 19950313 | | |
| | US 1997-967197 | A3 | 19971029 | | |

AB RAk[NHCH2CH2N(COCH2B)CH2CO]nQlQ1 (R = H, alkanoyl, alkoxycarbonyl, cycloalkanoyl, aroyl, heteroaroyl, group which promotes intracellular uptake or interacts with target nucleic acids; A, Q = amino acid residue; Q1 = OH, amino; B = nucleobase or prodrug form thereof; l = 0-20; n = 1-50), were prepd. by solid phase synthesis. Thus, H-[Aeg(T)]8-Lys-NH2 [ Aeg(T) = N-(2-aminoethyl)-N-[(1-thyminyl)acetyl]glycyl] was prepd. by coupling of FMOC-Lys(BOC)-OH and FMOC-Aeg(T)-OH (prepn. given) on 5-(FMOC-amino-4-methoxybenzyl)-2,4-dimethoxyphenylpropionic acid-derivatized aminomethylpolystyrene resin using an activator soln. of PyBOP (PyBOP = benzotriazolyl-1-oxytripyrrolidiniophosphonium hexafluorophosphate) in DMF, NEM (N-ethylmorpholine) in DMF as base for activation, and 20% piperidine in DMF for deprotection.

L50 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:994426 HCAPLUS
DN 124:87803
TI Preparation of substituted N-ethylglycine derivatives for the preparation of **peptide nucleic acids** and **peptide nucleic acid/deoxyribonucleic** acid hybrids.
IN **Breipohl, Gerhard; Uhlmann, Eugen**; Knolle, Jochen
PA Hoechst A.-G., Germany
SO Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 672661 | A1 | 19950920 | EP 1995-103333 | 19950308 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | DE 4408534 | A1 | 19950928 | DE 1994-4408534 | 19940314 |
| | FI 9501128 | A | 19950915 | FI 1995-1128 | 19950310 |
| | AU 9514799 | A1 | 19950921 | AU 1995-14799 | 19950310 |
| | AU 686729 | B2 | 19980212 | | |
| | CA 2144474 | AA | 19950915 | CA 1995-2144474 | 19950313 |
| | NO 9500959 | A | 19950915 | NO 1995-959 | 19950313 |
| | US 6075143 | A | 20000613 | US 1995-402840 | 19950313 |
| | JP 07258222 | A2 | 19951009 | JP 1995-54643 | 19950314 |
| | US 6465650 | B1 | 20021015 | US 2000-506901 | 20000218 |
| PRAI | DE 1994-4408534 | A | 19940314 | | |
| | US 1995-402840 | A3 | 19950313 | | |

OS MARPAT 124:87803
AB PGXCH2CH2N(COYB)CH2CO2H [PG = urethane- or trityl-type protecting group labile to weak acid; X = NH, O, S; Y = CH2, NH, O; B = (protected) nucleoside (replacement) base], were prepd. Thus, N-[(4-methoxyphenyl)diphenylmethyl]aminoethylglycine Me ester (prepn. given) in DMF was treated sequentially with 3,4-dihydro-4-oxo-1,2,3-benzotriazine,

4-ethylmorpholine, N4-benzoyl-N1-carboxymethylcytosine in DMF, and with DCC; the mixt. was stirred 20 h at room temp. to give the coupling product, which was sapond. with aq. NaOH/dioxane to give N-[(4-methoxyphenyl)diphenylmethyl]aminoethyl-N-[[1-(N4-benzoyl)cytosyl]acetyl]glycine.

L50 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:908968 HCAPLUS
DN 124:117857
TI The synthesis of polyamide nucleic acids using a novel monomethoxytrityl protecting-group strategy
AU **Will, David W.**; **Breipohl, Gerhard**; Langner, Dietrich; Knolle, Jochen; **Uhlmann, Eugen**
CS Hoechst AG, Allgemeine Pharma Forschung G838, Frankfurt am Main, D-65926, Germany
SO Tetrahedron (1995), 51(44), 12069-82
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier
DT Journal
LA English
OS CASREACT 124:117857
AB The prepn. of 4-MeOC6H4CPh2NHCH2CH2N(COCH2R)CH2CO2Me (R = thymine, N4-tert-butylbenzoylcytosine, N6-anisoyladenine, N2-isobutanoylguanine) for the synthesis of polyamide nucleic acids (**PNAs**) is described. The use of base-labile acyl-type nucleobase protecting groups, including monomethyltrityl N-protection of H2NCH2CH2NhCH2CO2Me, and of a succinyl-linked solid-support offers a synthetic strategy similar to std. oligonucleotide synthesis conditions. This strategy has been successfully applied for the synthesis of **PNAs** of mixed base sequence.

L50 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2003 ACS
AN 1991:443507 HCAPLUS
DN 115:43507
TI Fusion proteins, their preparation and use
IN Stengelin, Siegfried; Ulmer, Wolfgang; Habermann, Paul; **Uhlmann, Eugen**; Seed, Brian
PA Hoechst A.-G., Germany; General Hospital Corp.
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9103550 | A1 | 19910321 | WO 1990-US4840 | 19900828 |
| | W: AU, CA, FI, HU, JP, KR, NO, US | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE | | | | |
| | IL 95495 | A1 | 19961016 | IL 1990-95495 | 19900827 |
| | CA 2065146 | AA | 19910301 | CA 1990-2065146 | 19900828 |
| | AU 9062872 | A1 | 19910408 | AU 1990-62872 | 19900828 |
| | AU 638277 | B2 | 19930624 | | |
| | EP 489780 | A1 | 19920617 | EP 1990-912715 | 19900828 |
| | EP 489780 | B1 | 19981104 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE | | | | |
| | HU 60327 | A2 | 19920828 | HU 1992-674 | 19900828 |
| | JP 05501799 | T2 | 19930408 | JP 1990-512297 | 19900828 |
| | JP 3043803 | B2 | 20000522 | | |
| | AT 173018 | E | 19981115 | AT 1990-912715 | 19900828 |
| | ES 2124216 | T3 | 19990201 | ES 1990-912715 | 19900828 |
| | HU 216069 | B | 19990428 | HU 1974-92006 | 19900828 |
| | ZA 9006839 | A | 19910626 | ZA 1990-6839 | 19900928 |
| | NO 9200774 | A | 19920428 | NO 1992-774 | 19920227 |
| | US 5227293 | A | 19930713 | US 1992-838221 | 19920423 |

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|---|---|---|---|---|---|
| | US 5358857 | A | 19941025 | US 1993-73508 | 19930609 |
| PRAI | US 1989-399874 | A2 | 19890829 | | |
| | WO 1990-US4840 | A | 19900828 | | |
| | US 1992-838221 | A1 | 19920423 | | |

OS MARPAT 115:43507

AB A process for prepg. a fusion protein comprising a ballast **peptide** or protein and a desired protein consists of (1) constructing an **oligonucleotide** mixt. which encodes the ballast **peptide** /protein; (2) creating a gene bank by inserting the **oligonucleotide** mixt. into a vector such that it is functionally linked to a regulatory region and to the gene encoding the desired protein; (3) transforming host cells with the vectors, and selecting clones which produce the fusion protein in high yield. The **oligonucleotide** encoding the ballast **peptide**/protein comprises (DCD)x (D = A,G,T; x = 4-12). An example of such an oligonucleotide which was used to produce a proinsulin-contg. fusion protein in Escherichia coli is ATGGCD(DCD)yACGCGT (y = 3-6). The ballast peptide/protein does not interfere with folding of the desired protein, and is designed to produce a fusion protein which is sol. or easily solubilized.

L50 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2003 ACS

AN 1988:1549 HCAPLUS

DN 108:1549

TI Chemoenzymic synthesis of genes encoding medium-sized **polypeptides** by use of only one synthetic **oligonucleotide**

AU **Uhlmann, Eugen**; Hein, Friedrich

CS Hoechst A.-G., Frankfurt/Main, D-6230/80, Fed. Rep. Ger.

SO Nucleic Acids Symposium Series (1987), 18(Symp. Chem. Nucleic Acid Compon., 7th, 1987), 237-40
CODEN: NACSD8; ISSN: 0261-3166

DT Journal

LA English

AB A novel strategy for the synthesis of genes encoding medium-sized **polypeptides** from only one synthetic **oligodeoxynucleotide** is outlined. A 140-mer oligodeoxynucleotide forming a hairpin structure at its 3'-end was synthesized and successfully used in the construction and cloning of a gene coding for salmon calcitonin-gly (33). Employing this "one oligonucleotide - one gene" approach, the manual work required for oligodeoxynucleotide synthesis is reduced to a min.

L50 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2003 ACS

AN 1986:436849 HCAPLUS

DN 105:36849

TI Synthetic signal sequence for transport of proteins in expression systems

IN Engels, Joachim; Leineweber, Michael; **Uhlmann, Eugen**; Wetekam, Waldemar

PA Hoechst A.-G. , Fed. Rep. Ger.

SO Ger. Offen., 22 pp.
CODEN: GWXXBX

DT Patent

LA German

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | DE 3436818 | A1 | 19860410 | DE 1984-3436818 | 19841006 |
| | EP 177827 | A2 | 19860416 | EP 1985-112043 | 19850923 |
| | EP 177827 | A3 | 19871202 | | |
| | EP 177827 | B1 | 19931118 | | |
| | R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| | AT 97445 | E | 19931215 | AT 1985-112043 | 19850923 |
| | HU 40164 | A2 | 19861128 | HU 1985-3761 | 19850930 |
| | HU 197355 | B | 19890328 | | |

| | | | | | |
|---|---|---|---|---|---|
| | JP 61088883 | A2 | 19860507 | JP 1985-221120 | 19851003 |
| | ES 547600 | A1 | 19860316 | ES 1985-547600 | 19851004 |
| | DK 8504532 | A | 19860407 | DK 1985-4532 | 19851004 |
| | AU 8548333 | A1 | 19860410 | AU 1985-48333 | 19851004 |
| | AU 595486 | B2 | 19900405 | | |
| | IL 76573 | A1 | 19920621 | IL 1985-76573 | 19851004 |
| | CA 1340280 | A1 | 19981222 | CA 1985-492345 | 19851004 |
| PRAI | DE 1984-3436818 | | 19841006 | | |
| | EP 1985-112043 | | 19850923 | | |

AB A synthetic signal peptide-coding DNA sequence is prepd. which contains endonuclease cleavage sites to permit its insertion into expression vectors. Coupling of a protein-coding gene with this sequence in the vector results in expression of the protein fused to the signal peptide, and in transport of the protein out the cell. For example, the signal DNA sequence for Escherichia coli alk. phosphatase was prepd. by ligation of synthetic oligonucleotides. A DNA was prepd. which contained a synthetic regulatory region (promoter, lac operator, ribosomal binding site) a recognition sequence for EcoRI, the signal DNA sequence, and the gene for proinsulin for cloning and expression in E. coli. The expressed proinsulin was secreted by cells.

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MOST RECENT DERWENT UPDATE: 200324 <200324/DW>
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available in the /ABEX field. An additional search field
/BIX is also provided which comprises both /BI and /ABEX <<<

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GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

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L61 ANSWER 1 OF 1 WPIX (C) 2003 THOMSON DERWENT
AN 2002-075055 [10] WPIX
DNC C2002-022297
TI New peptide nucleic acid derivatives, useful e.g. for tumor treatment and diagnosis, contain terminal, deprotonizable phosphoryl groups for e.g. improved solubility.
DC B04 D16
IN BREIPOHL, G; UHLMANN, E; WILL, D W
PA (AVET) AVENTIS PHARMA DEUT GMBH; (BREI-I) BREIPOHL G; (UHLM-I) UHLMANN E; (WILL-I) WILL D W
CYC 96
PI WO 2001079216 A2 20011025 (200210)* DE 93p C07H000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

DE 10019135 A1 20011031 (200210) C07K007-00
AU 2001054795 A 20011030 (200219) C07H000-00
US 2002187473 A1 20021212 (200301) C12Q001-68 <--
NO 2002004959 A 20021015 (200305) C07H000-00
EP 1276760 A2 20030122 (200308) DE C07K014-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001010110 A 20030211 (200317) C07K014-00

ADT WO 2001079216 A2 WO 2001-EP4030 20010407; DE 10019135 A1 DE 2000-10019135 20000418; AU 2001054795 A AU 2001-54795 20010407; US 2002187473 A1 US 2001-835371 20010417; NO 2002004959 A WO 2001-EP4030 20010407, NO 2002-4959 20021015; EP 1276760 A2 EP 2001-927897 20010407, WO 2001-EP4030 20010407; BR 2001010110 A BR 2001-10110 20010407, WO 2001-EP4030 20010407

FDT AU 2001054795 A Based on WO 200179216; EP 1276760 A2 Based on WO 200179216; BR 2001010110 A Based on WO 200179216

PRAI DE 2000-10019135 20000418

IC ICM C07H000-00; C07K007-00; C07K014-00; C12Q001-68
ICS A61K038-00; A61K048-00; C07F009-40; C07K001-04; C07K017-02; C12Q001-02; C12Q001-70; G01N033-563; G01N033-569; G01N033-58

AB WO 200179216 A UPAB: 20020213

NOVELTY - New PNA (peptide nucleic acid) derivatives (A) having at the C-, optionally also the N-, terminus one or more phosphoryl (including oxo-, thiono- or imino-phosphoryl) groups, at least one of which contains one or more deprotonizable groups, preferably hydroxy or mercapto.

DETAILED DESCRIPTION - New PNA (peptide nucleic acid) derivatives (A) having at the C-, optionally also the N-, terminus one or more phosphoryl (including oxo-, thiono- or imino-phosphoryl) groups, at least one of which contains one or more deprotonizable groups, preferably hydroxy or mercapto. The phosphoryl groups are attached to the PNA backbone directly or through a spacer, by an oxygen-, sulfur- or nitrogen-phosphorus bond.

INDEPENDENT CLAIMS are also included for the following:

(1) detection reagent containing (A);

(2) PNA chip containing (A);

(3) biosensor containing (A);

(4) pharmaceutical composition containing (A) and optionally other additives and/or carriers;

(5) antisense, antigene, decoy or chimeraplast agents containing (A); and

(6) method for preparing (A).

ACTIVITY - Cytostatic; virucide; dermatological; antiasthmatic.

No biological data given.

MECHANISM OF ACTION - Inhibiting transcription or translation by hybridization.

No biological data given.

USE - (A) are useful for treatment of tumors (claimed) or (disclosed) generally any disease associated with (over)expression of particular genes, e.g. viral infection, vitiligo or other pigmentation disorders, and asthma; as diagnostic reagents; for detecting microorganisms and/or viruses; for detecting and/or quantifying nucleic acid; as reagents for (fluorescent) in-situ hybridization; as antisense, antigene, decoy or chimeraplast agents; and as molecular beacons.

ADVANTAGE - (A) can be produced in high yield and have improved solubility in water (particularly for lipophilic compounds), binding properties (affinity for complementary DNA or RNA) or cellular uptake, compared with uncharged PNAs. The ionizable groups allow them to be purified efficiently and also they migrate in electrical fields for microlocalization and concentration. A PNA targeted to the mRNA of Ha-ras having N-terminal phosphoryl, as mono-hexadecyl ester, and C-terminal 6-(phosphoryl)hexylamino (with fluorescein linked to phosphoryl) inhibited

growth of pre-B leukemia cells (DSM ACC 22) more effectively than the corresponding phosphorothioate oligonucleotide (no figures given).
Dwg.0/9

FS CPI

FA AB; GI; DCN

MC CPI: B04-E02; B04-E06; B04-E10; B04-F01; B04-F11; B12-K04A4; B12-K04E; B14-A02; B14-H01B; B14-K01A; B14-N17; D05-H09; D05-H12

TECH UPTX: 20020213

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compounds: The spacer is an alkanoylamide, poly(alkoxy)carboxamide or amino acid. At least one phosphoryl group contains at least one hydroxy or mercapto that is deprotonized at pH 4.5-14, best 6.5-9, and is particularly a (thio)phosphate, phosphonate or phosphoramidate. It may be substituted by one or more labels, crosslinkers, groups that improve intracellular uptake or increase binding affinity for nucleic acid. Preferred (A) are of formula (I), or their salts.

where

q = 0 or 1;

each D' = hydroxy, mercapto, amino, alkylamino or acylamino;

each V, W and W' = oxygen, sulfur or NR1;

each V' = V or U-(CR3R4)u'-CONH or U-(CH2CH2O)u'-CH2CONH;

each U = oxygen, sulfur or NH;

u' = 1-10;

each Y and Y' = hydroxy, mercapto, oxyanion, thioate or NR1R2;

each X and X' = U(2-22C alkanediyl)U or U(CH2CH2O)u' or a functional group;

each Z' and Z'' = hydroxy, mercapto, oxyanion, thioate or NR1R2, 1-22C alkyl, aryl(1-8C)alkyl, 1-22C alkyl-U, hydroxy(1-18C)-U, aminoalkyl-U or mercaptoalkyl-U, or a functional group;

R1 and R2 = hydrogen or 1-6C alkyl;

R3 and R4 = hydrogen, 1-6C alkyl or amino acid sidechain, or together, in V', form a 5-8C cycloalkyl;

n and m = 0-10;

POLY = the group ((-BLOCK-CONH)z''-BLOCK-G-);

each BLOCK = any of 9 PNA-type residues;

z'' = 0-100;

G = any of several linking groups providing at least one Y, Y', Z or Z' is a hydroxy, mercapto, oxyanion, or thioate and at least one BLOCK must contain a nucleobase.

Functional groups for X and Z are labels, crosslinkers or groups that increase binding affinity or intracellular uptake.

Particularly (A) is directed against part of a tumor suppressor gene, oncogene or telomerase, or their transcription products, specifically against the translation initiation site of HA-ras mRNA. About 50 sequences for (A) are reproduced.

Preparation: The C-terminus of an amido-nucleic acid (ANA) is coupled to a phosphorylation reactant, on a solid phase, or a C-terminal phosphorylated ANA is coupled to a solid phase. The backbone of the PNA is extended by sequential coupling of ANA monomers, and optionally the N-terminus phosphorylated. Preferred carriers are controlled pore glass, a 'Tentacle' gel or aminomethylpolystyrene. The product can be purified by chromatography or electrophoresis, exploiting the acidic nature of the phosphoryl group, particularly using a basic stationary phase (anion exchanger or mixed mode material) and a gradient of acidic or salt-containing eluant.

ABEX UPTX: 20020213

SPECIFIC COMPOUNDS - Preparation of 7 (A) is described, e.g. MeCONH(CH2CH2N(COCH-2B)-CH2CONH)11-(CH2)6-O-P(=O)(O-)2 where the sequence of B is 5'-TATTCCGTCAT.

ADMINISTRATION - (A) are administered rectally, parenterally, orally etc., typically at 0.01-50 mg/kg/day.

EXAMPLE - A bis(hydroxyethyl)sulfonyl-derivatized glass carrier was reacted with a phosphoramidite that included a 6-(protected amino)hexyl linker, then the product oxidized (iodine) and essentially conventional synthesis of peptide nucleic acid (PNA) carried out. Free amino groups were blocked by acetylation then the product recovered by treatment with concentrated ammonia (deprotection and release from the carrier) and purified on a C18 column to give MeCONH(CH2CH2N(COCH-2B)-CH2CONH)11-(CH2)6-O-P(=O)(O-)2 where the sequence of B is 5'-TATTCCGTCAT.

=> d his

(FILE 'REGISTRY' ENTERED AT 11:48:48 ON 12 APR 2003)
DEL HIS
L1 STR
L2 STR
L3 STR L2
L4 50 S L3
L5 1080 S L3 FUL
SAV L5 SIEW835/A
L6 STR L2
L7 0 S L6 CSS SAM SUB=L5
L8 0 S L6 CSS FUL SUB=L5
SAV L8 SIEW835A/A
L9 1 S L1 SAM SUB=L5
L10 57 S L1 FUL SUB=L5
SAV L10 SIEW835B/A
L11 2 S L10 AND 6/NR
L12 2 S L10 AND 7/NR
L13 1 S L11 NOT OC5-C6/ES
L14 1 S L12 NOT 46.150.18/RID
L15 208 S L5 AND P/ELS
L16 122 S L15 AND 1/P
L17 4 S L16 AND 1/NR

FILE 'REGISTRY' ENTERED AT 12:00:37 ON 12 APR 2003

FILE 'HCAPLUS' ENTERED AT 12:01:57 ON 12 APR 2003
L18 7 S L13,L14,L17
L19 3 S L18 AND (UHLMANN ? OR BREIPOHL ? OR WILL D?)/AU
L20 3 S L18 AND HOECHST?/PA,CS
L21 3 S L19,L20
E US20020187473/PN
L22 1 S E3
SEL RN

FILE 'REGISTRY' ENTERED AT 12:04:30 ON 12 APR 2003
L23 63 S E1-E63
L24 0 S L23 AND L5
L25 0 S L23 NOT SQL/FA
L26 2 S L23 NOT UNSPECIFIED
L27 61 S L23 NOT L26
L28 11 S L27 AND PEPTIDE
L29 5 S L28 AND 22/SQL
L30 6 S L28 NOT L29
L31 4 S L30 NOT ISOBENZOFURAN
L32 3 S L31 NOT THIENO
L33 50 S L27 NOT L28

FILE 'HCAPLUS' ENTERED AT 12:14:20 ON 12 APR 2003
E HID
E UHLMANN E/AU
L34 179 S E3,E4,E14-E18

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                E UEHLMANN E/AU
                E BRIEPOHL G/AU
                E BREIPOHL G/AU
L35          106 S E3-E6
                E BREIPOEHL G/AU
L36            1 S E2
                E WILL D/AU
L37           40 S E3,E7-E10
L38          275 S L34-L37
L39          274 S L38 NOT L22
                E PEPTIDE NUCLEIC ACID/CT
                E E4+ALL
L40         1717 S E3+NT
                E E2+ALL
L41         4496 S PEPTIDE(S)NUCLEIC ACID
L42         5022 S PNA
L43         8250 S L40-L42
L44        38606 S ?PEPTIDE?(S)(?NUCLEO? OR ?NUCLEI?)
L45        42349 S L43,L44
L46           37 S L38 AND L45
L47            7 S L18-L22 AND L45
L48            3 S L47 AND L38
L49            8 S L18-L22,L47,L48
L50           34 S L46 NOT L49
L51           41 S L18-L21,L46-L50 NOT L22

     FILE 'REGISTRY' ENTERED AT 12:24:29 ON 12 APR 2003

     FILE 'HCAPLUS' ENTERED AT 12:24:29 ON 12 APR 2003
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L52          SEL L51 1- RN :     657 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 12:24:30 ON 12 APR 2003
L53          657 S L52
L54          134 S L53 AND PEPTIDE AND NUCLEIC ACID
L55           90 S L54 NOT COMPLEX
L56            7 S L55 AND 6-7/NR
L57            5 S L56 NOT L13,L14,L17
L58           83 S L55 NOT L56
L59           43 S L58 NOT OH
L60           42 S L59 NOT XANTHEN?

     FILE 'HCAPLUS' ENTERED AT 12:28:50 ON 12 APR 2003

     FILE 'WPIX' ENTERED AT 12:29:13 ON 12 APR 2003
                E US20020187473/PN
L61            1 S E3

     FILE 'DPCI' ENTERED AT 12:29:54 ON 12 APR 2003
                E US20020187473/PN

     FILE 'WPIX' ENTERED AT 12:30:12 ON 12 APR 2003
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